Protocol ARQ-151-313

A Phase 3, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.15% and ARQ-151 Cream 0.05% in Subjects with Atopic Dermatitis

Sponsor: Arcutis Biotherapeutics, Inc.
3027 Townsgate Road, Suite #300
Westlake Village, CA 91361

Sponsor Representative: [redacted]

IND Number: [redacted]

Protocol Version: Amendment 1

Date: 17 September 2021

GCP Statement

This study is to be performed in full compliance with the protocol, International Conference on Harmonisation Good Clinical Practices (ICH GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

STUDY SITE INVESTIGATOR SIGNATURE PAGE

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ISSUE DATE: 17 September 2021

I have read this protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the current International Conference on Harmonisation Good Clinical Practices (ICH GCPs) and applicable local and regional regulations.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Arcutis Biotherapeutics, Inc. will discuss the material with them to ensure that they are fully informed about ARQ-151 and the study.

I agree that I or my designee will completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements. I will be responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Investigational Site Name: _____

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

SUMMARY OF CHANGES

The following sections have been changed in Amendment 1 of the ARQ-151-313 protocol:

Version/Date	Description
December 20, 2020	Original Protocol
Amendment 1 September 17, 2021	• Added Summary of Changes section. • Added statement that during the conduct of the study, additional countries and/or sites may be added if necessary. • Sample size increased from approximately 400 to approximately 1500 subjects to allow: – All subjects from ARQ-151-315 to enroll into the ARQ-151-313 Open Label Extension study. – An additional ~275 subjects ages 6-17 from ARQ-151-311 and additional ~275 subjects ages 6-17 from ARQ-151-312 to enroll into the ARQ-151-313 Open Label Extension study for a 24-week treatment period. This is Cohort-Week 24. • Clarification added that if an unscheduled visit is required for reasons other than safety, the following assessments are not required: – vIGA-AD and EASI – BSA affected with AD – Local tolerability assessment (by Investigator) • Removed all safety labs for subjects ages 2-11; safety labs would have been evaluated at screening in the preceding study and the investigator may order safety labs at any time during the study to evaluate an adverse event. • WI-NRS: – Added statement that caregiver/parents will be given instructions on how to complete this questionnaire for subjects between 2 and 5 years of age. – Added that parent and/or guardian will be trained at the baseline visit to assist the subject, if needed, in the accurate completion of the WI-NRS for subjects ≥ 6 years of age. • Added clarification that only subjects 18 years and older will be enrolled at sites located in the province of Québec in Canada.

Version/Date	Description
	• Added PK draw at Week 52/ET for subjects ≥ 12 years of age. • Updated exclusion criterion 5 and Figure 1 to note that subjects who have undergone a bilateral tubal ligation/occlusion are considered females of childbearing potential using a highly effective method of contraception. • Updated the language of endpoints to be consistent with other Arcutis study protocols • Added secondary endpoint: vIGA-AD success (defined as Viga-AD value of 0 or 1 plus a 2-grade improvement from baseline) • Removed some of the analyses and will add the details into SAP. – For the analysis for WI-NRS and EASI, the analysis changed to summary by visits overtime which includes change and percent change from baseline. – Removed the following duplicate sections: **Adverse Events:** The subject incidence of treatment-emergent adverse events (TEAE) will be summarized overall, by severity, and by attribution. **Clinical Laboratory Results:** Shifts in clinical laboratory parameters from baseline to worst post-baseline grade will be provided. • Moved the vital signs in Section 6.6 to Section of 6.9.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
α	Alpha Level (significance level)
AE	Adverse Event
AMP	Adenosine Monophosphate
AD	Atopic Dermatitis
AUC	Area Under the Curve
BSA	Body Surface Area
CDI	Children's Depression Inventory
CDLQI	Children's Dermatology Life Quality Index
C_{max}	Maximum Concentration
cm	Centimeter
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DFI	Dermatitis Family Impact
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
hr	Hour
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IGA	Investigator Global Assessment
IL	Interleukin

Abbreviation	Definition
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
kg	Kilogram
LED	Light Emitting Device
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
ng	Nanogram
P-450	Cytochrome P450
PDE-4	Phosphodiesterase 4
PDMP	Protocol Deviation Management Plan
PHQ-8	Patient Health Questionnaire-8
PI	Principal Investigator
PK	Pharmacokinetics
POEM	Patient-Oriented Eczema Measure
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCPS	Tri-Council Policy Statement

Abbreviation	Definition
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach Maximum Concentration
US	United States
vIGA-AD	Validated Investigator Global Assessment-Atopic Dermatitis
WI-NRS	Worst Itch – Numeric Rating Score

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Arcutis Biotherapeutics, Inc.		
Name of Investigational Product: ARQ-151 will be supplied as an emollient cream at 0.15% or 0.05% strength		
Name of Active Ingredient: Roflumilast, a PDE-4 inhibitor		
Protocol Number: ARQ-151-313	**Phase:** 3	**Country:** US and Canada
Title of Study: A Phase 3, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.15% and ARQ-151 Cream 0.05% in Subjects with Atopic Dermatitis		
Clinical Indication: Atopic Dermatitis		
Number of Sites: Up to approximately 120 study sites in the United States and Canada. During the conduct of the study, additional countries and/or sites may be added if necessary.		
Study Population: Up to approximately 1500 subjects that have completed the 4-week treatment period in studies ARQ-151-311 or ARQ-151-312 or ARQ-151-315 and are willing and qualified to enroll in this long-term extension study will receive ARQ-151 cream 0.15% (ARQ-151-311/312 roll-overs) or ARQ-151 cream 0.05% (ARQ-151-315 roll-overs) QD. Subjects 6-17 years of age enrolled under Amendment 1 will be treated for 24 weeks with ARQ-151 cream 0.15% (Cohort-Week 24). Subjects on ARQ-151 cream 0.05% who turn 6 years old during ARQ-151-313 will switch to ARQ-151 cream 0.15% at their first scheduled post-birthday visit.		
Objectives: **Primary:** To assess long-term safety in a multicenter, open-label, single-arm study in subjects with atopic dermatitis treated with ARQ-151 cream 0.15% QD (subjects ≥ 6 years of age) or ARQ-151 cream 0.05% QD (subjects 2 to 5 years of age) after completing one of three Phase 3 studies (ARQ-151-311, ARQ-151-312, or ARQ-151-315).		
Summary of Study Design: ARQ-151-313 is an open-label, single-arm, long-term safety study of ARQ-151 cream 0.15% and ARQ-151 cream 0.05% in subjects with atopic dermatitis. Eligible subjects will enroll into the long-term safety study on the same day as the Week 4 visit of the preceding study (ARQ-151-311, ARQ-151-312, or ARQ-151-315). Study medication will be applied topically for up to 24 (Cohort-Week 24) or 52 weeks at home. All affected areas, except on the scalp, will be treated. For the first 4 weeks of study ARQ-151-313, <u>all</u> subjects will apply study medication QD in the areas identified and treated as per the body diagram in the preceding study (ARQ-151-311/312/315). Beginning at the Week 4 visit, any subject who achieves vIGA-AD of '0-clear' as confirmed by the Investigator at a scheduled or unscheduled clinic visit, will switch to twice weekly (BIW) maintenance treatment. For maintenance therapy, study medication will be applied on two nonconsecutive days per week (e.g. Monday and Thursday) to areas commonly and/or most recently affected by AD, and any		

areas where AD is developing. Subjects receiving maintenance treatment who experience AD worsening (signs and symptoms) for 1 week despite dosing twice weekly will phone the clinical study site, resume daily dosing, and complete the subject diary accordingly. The phone call (but not a clinic visit) is required to resume daily dosing. At clinic visits, subjects receiving maintenance treatment may continue twice weekly maintenance dosing if vIGA-AD is either '0-clear' or '1-almost clear'. Subjects will resume daily dosing if vIGA-AD ≥2, and can resume daily dosing if signs/symptoms of AD are not adequately controlled with maintenance therapy despite vIGA-AD of '1-almost clear'. Periodic clinic visits will include assessments for clinical safety, tolerability, and disease severity.

Sample Size Justification:

The sample size will provide a sufficient number of subjects to evaluate the long-term safety of ARQ-151 cream 0.15% or ARQ-151 cream 0.05% over 24 or 52 weeks of treatment, and in combination with other studies will provide the development program with sufficient numbers of subjects to meet ICH E1A safety exposure goals.

Number of Patients (planned):

Up to approximately 1500 subjects are planned to be enrolled in this study.

Duration of Treatment:

Approximately 24 (Cohort-Week 24) or 52 weeks

Main Criteria for Inclusion:

1. For adult subjects: Participants legally competent to sign and give informed consent. For pediatric and adolescent subjects: Informed consent of parent(s) or legal guardian, and, if age appropriate, assent by the subjects, as required by local laws.
2. Males and females, ages 2 years and older. (Only subjects 18 years and older will be enrolled at sites located in the province of Québec in Canada.)
3. Subjects with atopic dermatitis who met eligibility criteria for and successfully completed ARQ-151-311 or ARQ-151-312 or ARQ-151-315 through Week 4, and are able and eligible to enroll into this long-term safety study on the Week 4 visit of the preceding study.
4. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at all study visits. In addition, sexually active FOCBP must agree to use at least one form of a highly effective or barrier method of contraception throughout the trial. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active.
5. Females of non-childbearing potential should either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status would have been confirmed with FSH testing in the preceding study) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
6. Subjects and parent(s)/legal guardian(s) are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

Main Criteria for Exclusion:

1. Subjects who experienced a treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-151 cream in studies ARQ-151-311 or ARQ-151-312 or ARQ-151-315.
2. Subjects that use any Excluded Medications and Treatments (see Table 2).
3. Subjects with skin conditions other than AD that would interfere with evaluations of the effect of the study medication on AD, as determined by the Investigator. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements (e.g., molluscum contagiosum).
4. Subjects with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.
5. Known allergies to excipients in ARQ-151 cream [redacted]
6. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin during the study period.
7. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin during the study period.
8. Known or suspected:
   a. Severe renal insufficiency (defined as calculated creatinine clearance < 30mL/min)

   Refer to the creatinine levels from the following visits:
   - ARQ-151-311/ARQ-151-312 studies: Screening Visit for subjects ages 6-11 and Baseline/Day 1 for subjects ≥12 years old (for subjects 12-18 years old, if screening lab tests were collected within 3 weeks of Baseline/Day 1, screening results will be used)
   - ARQ-151-315 study: Screening Visit

   b. Moderate to severe hepatic disorders (Child-Pugh B or C)
   c. History of severe depression, suicidal ideation or behavior
9. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
10. Subjects with any known serious medical condition (e.g., uncontrolled hypo- or hyper-thyroidism) or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
11. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication.
12. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
13. Subjects and parent(s)/legal guardian(s) who are unable to communicate, read or understand the local language(s), or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.
14. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects (subjects enrolled in other studies of ARQ-151) living in the same house.

Investigational Product, Dosage and Mode of Administration:

For the first 4 weeks of study ARQ-151-313, all subjects will apply study medication QD in the areas identified and treated as per the body diagram in the preceding study (ARQ-151-311/312/315). Beginning at the Week 4 visit, any subject who achieves vIGA-AD of '0-clear' as confirmed by the Investigator at a scheduled or unscheduled clinic visit, will switch to twice weekly (BIW) maintenance treatment. For maintenance therapy, study medication will be applied on two nonconsecutive days per week (e.g. Monday and Thursday) to areas commonly and/or most recently affected by AD, and any areas where AD is developing. Subjects receiving maintenance treatment who experience AD worsening (signs and symptoms) for 1 week despite dosing twice weekly will phone the clinical study site, resume daily dosing, and complete the subject diary accordingly. The phone call (but not a clinic visit) is required to resume daily dosing. At clinic visits, subjects receiving maintenance treatment may continue twice weekly maintenance dosing if vIGA-AD is either '0-clear' or '1-almost clear'. Subjects will resume daily dosing if vIGA-AD ≥2, and can resume daily dosing if signs/symptoms of AD are not adequately controlled with maintenance therapy despite vIGA-AD of '1-almost clear'.

Key Assessments:

Safety will be monitored through local tolerability assessments, vital signs, physical examination, safety labs (subjects ≥12 years old), Children's Depression Inventory 2 (CDI-2, parent report for children 6-11 years old, inclusive), modified PHQ-A (for adolescents 12-17 years old, inclusive), PHQ-8 (for adults), C-SSRS (for adolescents and adults of 12 years old and older), and AEs. Parents/caregivers of subjects 2 to 5 years of age will be advised to promptly report any changes in behavior that could signal psychological distress or emotional distress.

Efficacy assessments will include vIGA-AD, EASI, WI-NRS, BSA, CDLQI/DLQI, DFI, IDQOL, SCORAD, and POEM.

Study Endpoints:

Primary:

- Adverse Events (AEs)
- Serious Adverse Events (SAEs)

Secondary:

- Validated Investigator Global Assessment-Atopic Dermatitis (vIGA-AD) value 0 or 1 at each assessment
- vIGA-AD success (defined as vIGA-AD value of 0 or 1 plus a 2-grade improvement from baseline)
- WI-NRS score over time
- EASI score over time

Criteria for Evaluation:

Safety:

The safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

The subject incidence of treatment-emergent adverse events (TEAE) will be summarized overall, by severity, and by attribution.

Statistical Methods:

Descriptive statistics will be presented for the endpoints and safety data collected in the clinical trial. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, Q1, Q3, minimum, and maximum for continuous data.

Adverse Events

For the primary endpoints, the occurrence of TEAEs and the occurrence of Serious Adverse Events (SAEs) will be tabulated by preferred term and system organ class.

In addition, summary tables of TEAEs by severity, by relationship to investigational product, and those leading to withdrawal from investigational product will be created.

Vital Signs

Descriptive statistics will be calculated for vital signs over time.

Clinical Laboratory Results

Descriptive statistics of the laboratory parameters will be calculated at each scheduled time point. Shifts from baseline will be tabulated.

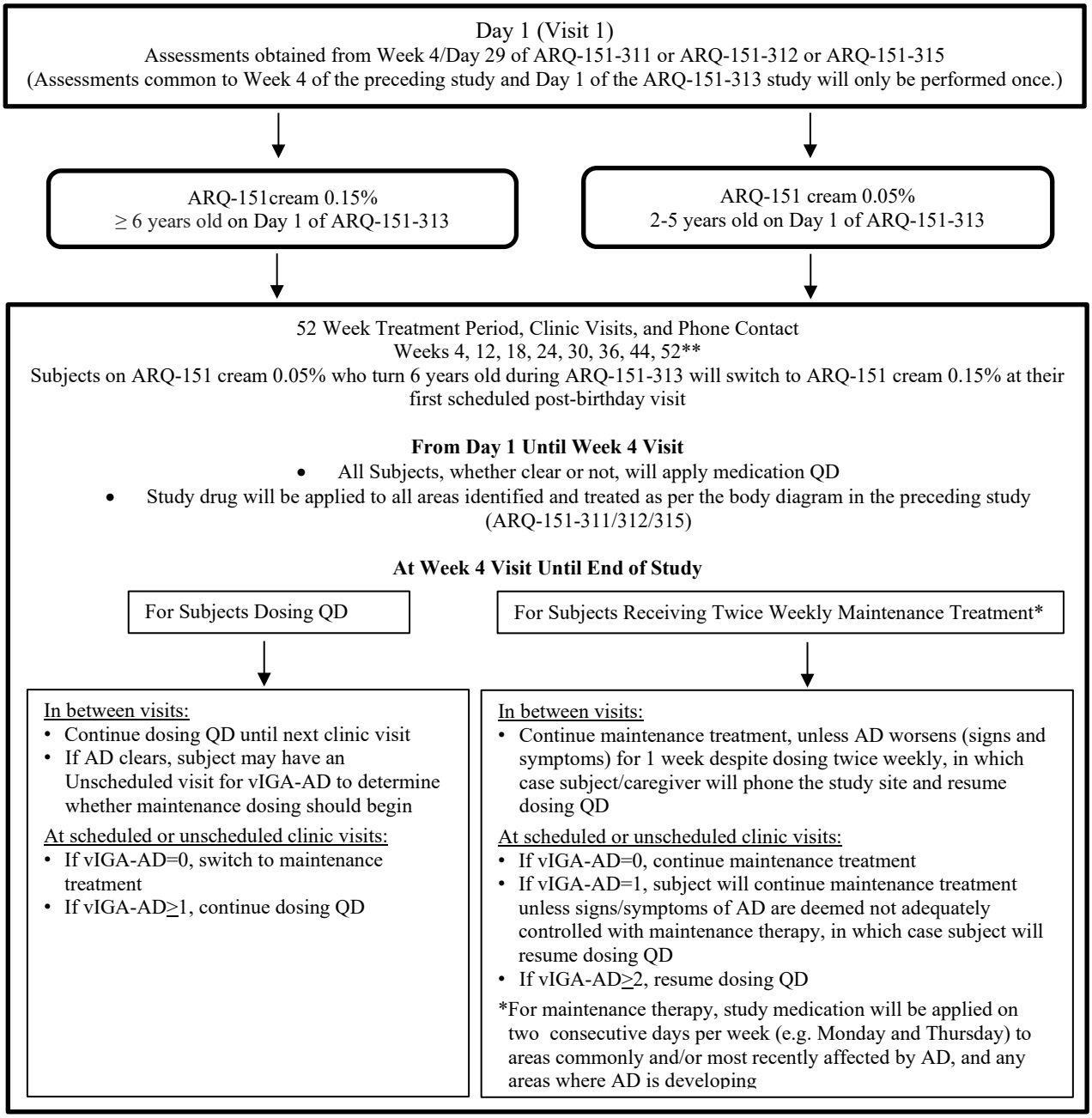
Patient Health Questionnaires

CDI-2 (in 6-11 year-olds), PHQ-8 (in adults), a modified version of the PHQ-A (in adolescents), and C-SSRS questionnaires (in adolescents and adults) will be completed at all study visits. Descriptive statistics will be calculated for the CDI-2, PHQ-8, and Modified PHQ-A. The C-SSRS will be analyzed per the Scoring and Data Analysis Guide from the Columbia Lighthouse Project.

Efficacy Assessments

Descriptive statistics will be presented for the efficacy data collected in the clinical trial for the subjects who enroll in this study and receive at least one day of study drug. For the binary and continuous endpoints related to vIGA-AD, WI-NRS, and EASI, descriptive statistics will be provided for the endpoints each scheduled visit.

1.2. Study Schema



** Under Amendment 1, 24 Week Treatment Period for Cohort-Week 24, Clinic Visits, and Phone Contact Weeks 4, 12, 18, 24

1.3. Schedule of Visits and Assessments

Study Procedure	Day 1	Wk 4	Wk 12	Wk18	Wk 24[t]	Wk 30	Wk 36	Wk 44	Wk 52/ET
Visit #	**1(Week 4) of ARQ-151-311 or ARQ-151-312 or ARQ-151-315**	**2**	**3**	**Phone Visit**	**4**	**Phone Visit**	**5**	**Phone Visit**	**6**
Visit Window		**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Informed consent/assent	X								
Physical examination[a]	X[s]	X			X				X
I/E criteria	X								
Hematology, Serum Chemistries, and Urine Analysis[b]	X[s]				X				X
Vital signs, height, weight[c]	X[s]	X	X		X		X		X
vIGA-AD, EASI, BSA, SCORAD[d]	X[s]	X	X		X		X		X
WI-NRS pruritus[e]	X[s]								
POEM[f]	X[s]	X	X		X		X		X
Local Tolerability Assessment[g]	X	X	X		X		X		X
CDI-2, PHQ-8, PHQ-A, C-SSRS[h]	X[s]	X	X		X		X		X
DLQI, CDLQI, IDQOL, DFI[i]	X[s]	X	X		X		X		X
Medical Photography[j]	X[s]	X	X		X		X		X
Urine pregnancy test[k]	X[s]	X	X		X		X		X
PK draws[l]									X

Study Procedure	Day 1	Wk 4	Wk 12	Wk18	Wk 24[t]	Wk 30	Wk 36	Wk 44	Wk 52/ET
Visit #	**1(Week 4) of ARQ-151-311 or ARQ-151-312 or ARQ-151-315**	**2**	**3**	**Phone Visit**	**4**	**Phone Visit**	**5**	**Phone Visit**	**6**
Visit Window		**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Dispense study medication kit[m]	X	X	X		X		X		
Drug application and Parents/Caregivers training in clinic	X								
Dispense/review diary[n]	X	X	X		X		X		X
Maintenance Dosing Determination[o]		X	X		X		X		
Weigh study medication[p]	X	X	X		X		X		X
Compliance Determination[q]		X	X		X		X		X
Adverse event assessment[r]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Study Exit					X[t]				X

[a] Limited physical examination: skin, lungs, and heart only

[b] Hematology, Serum Chemistries, and Urine Analysis will only be done in subjects ≥ 12 years of age at time of enrollment in the preceding study.

[c] Height will be collected at Day 1 only for subjects ≥18 years old and at every clinic visit for subjects <18 years old. Weight should be obtained using a calibrated weight scale and the same scale should be used for a subject throughout the duration of the study. The subject should remove shoes and heavy clothing (sweaters or jackets), and empty pockets. The subject should stand with both feet in the center of the scale with their arms at their side and hold still. Record the weight to the nearest decimal fraction (for example, 25.1 kilograms). For subjects <18 years of age, measure the weight in triplicate and report the average weight in EDC. A 5% or greater weight loss (whether or not intentional or otherwise explained) should be reported to the medical monitor.

[d] The vIGA-AD assessment will be a 5-point scale ranging from clear (0) to severe (4) and is evaluated for the entire body except the scalp, palms, and soles. EASI takes into account overall severity of erythema, infiltration/papulation, excoriation, and lichenification, in addition to extent of BSA affected. The 4 clinical signs will be graded on a 4-point scale (0 [absent] to 3 [severe]) for 4 body regions (head and neck, upper extremities, lower extremities, and trunk). Total EASI score will be calculated as a sum of scores of all 4 body regions. EASI total score will range from 0 (absent) to 72 (severe). Total BSA affected by AD will be determined for all body surfaces except the scalp, palms and soles. vIGA-AD should be completed prior to other physician assessments. SCORAD total score will range between 0 and 103.

Footnotes from table above:

[e] The WI-NRS pruritus questionnaire will be completed once a week at home utilizing a diary. **The WI-NRS will be self-reported by subjects for subjects ≥ 6 years of age, and reported by parent/guardian for subjects <6 years of age.** During the Phone Visits at Weeks 18, 30, and 44 a reminder will be given to subjects to complete the WI-NRS pruritis questionnaire once a week.

[f] POEM will be completed by all subjects either by self or by proxy completion (for children unable to read and/or understand the POEM questionnaire, the parent/guardian/caregiver will complete the questionnaire).

[g] At Day 1 only, local tolerability assessments should be recorded prior to study drug application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score) and 10-15 minutes post-drug application for the Subject's '0-3' burning/stinging assessment. **Note for investigator tolerability assessments: reactions at the site of product application should be differentiated from the preexisting inflammation associated with the subject's atopic dermatitis. For subject tolerability assessments after Day 1, the subject will assess burning/stinging (0-3 score) 10-15 minutes post drug application based on recall of the last drug application.** For subjects <6 years of age, parents will complete.

[h] Adolescents and adults (12 years and older) will complete the C-SSRS (12 years old of age and older). Adults will complete the PHQ-8. Adolescents (ages 12 to 17 years of age, inclusive) will complete the PHQ-A (PHQ-9 modified for Adolescents). Parents/caregivers will complete the parent report (CDI-2) for children 6-11 years of age, inclusive. Subjects will continue with the assessments specific to their age group at the time of consent/assent at Screening of the preceding study.

[i] The DLQI will be completed by subjects ≥17 years of age (based on age at start of preceding studies ARQ-151-311/312). The CDLQI will be completed for subjects ≥ 4 years of age and ≤16 years of age (based on age at start of preceding studies ARQ-151-311/312/315). The Infants' Dermatitis Quality of Life (IDQOL) will be completed by parents/caregivers for subjects < 4 years (based on age at start of parent preceding studies ARQ-151-315). The Dermatitis Family Impact Questionnaire (DFI) will be completed by parents/caregivers for all subjects ≥ 2 years of age and ≤17 years of age. Subjects will continue with the assessments specific to their age group at the time of consent/assent at Screening of the preceding study. DFI is not to be conducted for subjects who were ≤17 years of age in the ARQ-151-311/312 studies and turned 18 years of age prior to enrollment into ARQ-151-313.

[j] Photography will be performed using Canfield equipment on all subjects at all study sites. All efforts will be made to de-identify the subjects. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure and documented on the informed consent. See Photography Manual for details.

[k] A urine pregnancy test will be administered to all females of child-bearing potential. A negative result is required for continued participation in the study, and results must be available prior to dispensing of study drug at each visit.

[l] For all subjects ≥12 years old entering this study under Amendment 1 a single PK trough draw will be collected at Week 52/ET. Ensure study medication was not applied in the area where PK will be drawn.

[m] It is expected that kits will be dispensed based on %BSA affected and subject's age. Subjects who turn 6 years old during the study will switch to ARQ-151 cream 0.15% at their first scheduled post-birthday visit. See IP Handling Manual for details. Under Amendment 1, this is the final visit for Cohort-Week 24 and no kits will be dispensed at this visit.

[n] Dispensing of IP is allowed, if needed. Study site should review IP kit to ensure sufficient IP is available until the next visit and only dispense additional IP if needed. **All subjects will continue study medication application in the areas identified and treated as per the body diagram in the preceding study for the first 4 weeks of the current study (ARQ-151-313).**

Footnotes from table above:

[o] Beginning at the Week 4 visit, any subject who achieves vIGA-AD of '0-clear' as confirmed by the Investigator at a scheduled or unscheduled clinic visit, will switch to twice weekly (BIW) maintenance treatment. For maintenance therapy, study medication will be applied on two nonconsecutive days per week (e.g. Monday and Thursday) to areas commonly and/or most recently affected by AD, and any areas where AD is developing. Subjects receiving maintenance treatment who experience AD worsening (signs and symptoms) for 1 week despite dosing twice weekly will phone the clinical study site, resume daily dosing, and complete the subject diary accordingly. The phone call (but not a clinic visit) is required to resume daily dosing. At clinic visits, subjects receiving maintenance treatment may continue twice weekly maintenance dosing if vIGA-AD is either '0-clear' or '1-almost clear'. Subjects will resume daily dosing if vIGA-AD ≥2, and can resume daily dosing if signs/symptoms of AD are not adequately controlled with maintenance therapy despite vIGA-AD of '1-almost clear'. Under Amendment 1, maintenance dosing determination will not be conducted at Week 24 for Cohort-Week 24.

[p] The entire kit (every tube) should be weighed and recorded at every visit. See IP Handling Manual for details.

[q] Compliance calculation is described in the IP Handling Manual

[r] Any emergent AEs will be followed in the clinic for up to one month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

[s] This data will be obtained from Week 4 of ARQ-151-311/312/315 Study and used as the Day 1 data for this long-term safety study (ARQ-151-313).

[t] Under Amendment 1, this is the final visit for Cohort-Week 24 from ARQ-151-311 and ARQ-151-312.

2. INTRODUCTION

2.1. Background

Refer to the current ARQ-151 Investigator's Brochure (IB) for the most current PDE-4 dermal and oral/systemic nonclinical and clinical information.

Roflumilast is a phosphodiesterase 4 (PDE-4) inhibitor approved globally to reduce the risk of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis. Roflumilast and its active metabolite, roflumilast N-oxide, are high affinity selective inhibitors of PDE-4 (a major cyclic-3′,5′-adenosine monophosphate (cyclic AMP)-metabolizing enzyme), whose activity leads to accumulation of intracellular cyclic AMP. There are four different subtypes of PDE-4: PDE-4a, PDE-4b, PDE-4c, and PDE-4d, each with several isoforms (splicing variants). IC_{50} values of both roflumilast and roflumilast N-oxide for the different PDE-4 isoforms and subtypes are mostly sub-nanomolar and single digit nanomolar (Hatzelmann 2010). The PDE-4 family of enzymes are the most prevalent phosphodiesterases in immune cells and inhibition of PDE-4 subtypes has been associated with anti-inflammatory effects in many biological systems.

Atopic dermatitis is a chronic inflammatory skin disorder affecting children and adults, with the majority presenting with disease of mild to moderate severity. The use of topical corticosteroids and/or topical calcineurin inhibitors, in combination with emollients has been the mainstay for treating atopic dermatitis. Topical calcineurin inhibitors block the activation of T-lymphocytes and diminish inflammation, but are accompanied by a boxed warning for the development of lymphomas and other lymphoproliferative diseases. Topical corticosteroids can cause skin atrophy and hypothalamic-pituitary axis suppression, and their use is often accompanied by poor adherence due to a fear of using steroids termed corticosteroid phobia or corticophobia that has been documented in both healthcare providers and patients (Bos 2019).

More recently, Eucrisa® (crisaborole), a PDE-4 inhibitor was approved for the topical treatment of mild to moderate atopic dermatitis in patients 3 months of age and older. Eucrisa provides precedence for the effectiveness of topical PDE-4 inhibitors in atopic dermatitis, but it is a twice-daily ointment, its efficacy may be modest, and its use may be accompanied by burning, stinging, and local skin reactions. As a result, there is a need for the development of new topical products for the treatment of atopic dermatitis (Nygaard 2017).

The therapeutic use of PDE-4 inhibitors in AD is based on the recognized intracellular role of PDE-4 in keratinocytes (Dastidar 2007, Hanifin 1996). Circulating leukocytes in AD patients have PDE-4 activity, which has been associated with higher production of proinflammatory mediators and lower production of the anti-inflammatory mediator IL-10, in part due to hydrolyzation of cyclic adenosine monophosphate (cAMP) (Grewe 1982, Furue 2014, Baumer 2007). This consequently diminishes levels of cAMP, which leads to increased transcription of numerous cytokines, accelerating a number of intracellular functions involved in acute and chronic inflammation (Grewe 1982). Thus, targeting PDE-4 has been shown to directly attenuate inflammation due to inhibition of the breakdown of cAMP, consequently reducing the levels of tumour necrosis factor-α, IL-12, IL-23, and other signaling effectors (Murrell 2015, Nazarian 2009).

2.2. Nonclinical Studies

The safety profile of oral roflumilast is well-established. An extensive systemic toxicity program that evaluated both roflumilast and its active N-oxide metabolite in multiple species via the oral route of administration was conducted to support registration of the 500 µg tablet for COPD.

The previously-conducted systemic toxicity program included studies to evaluate reproductive toxicity, genotoxicity and carcinogenicity, and the results of those studies are included in the labeling for oral roflumilast (DALIRESP PI 2020).

To support the development of ARQ-151 topical cream, a GLP-compliant dermal toxicity program has been conducted. To date, no new risks have been identified through the dermal toxicity program. In 13-week dermal toxicity studies in mice and minipigs , and a 39-week dermal toxicity study in minipigs, no evidence of systemic toxicity was observed. The NOAEL in both studies was the 1% concentration of ARQ-151 cream (20 mg/kg), the highest dose administered and the maximum feasible concentration.

Local tolerance studies demonstrated ARQ-151 cream is not a skin sensitizer or eye irritant, and it does not have phototoxic potential.

Across the dermal and systemic toxicology programs, the exposure to parent drug and N-oxide metabolite differs by route and species. While exposure to roflumilast and its active metabolite are likely to be higher following topical administration of ARQ-151 cream relative to oral administration, when the margins from the toxicity studies are considered as a whole, the NOAELs across routes and species provide assurance that the anticipated exposures with ARQ-151 cream is safe.

2.3. Clinical Studies

2.3.1. Topical Roflumilast Cream

ARQ-151 cream has been evaluated in both plaque psoriasis (Phase 3 ongoing) and atopic dermatitis (through Phase 2). The 0.3% concentration is used in psoriasis and the 0.15% and 0.05% concentration are used in atopic dermatitis. The safety data from the psoriasis studies are relevant to the atopic dermatitis development program.

2.3.1.1. Psoriasis Phase 2a (ARQ-151-101)

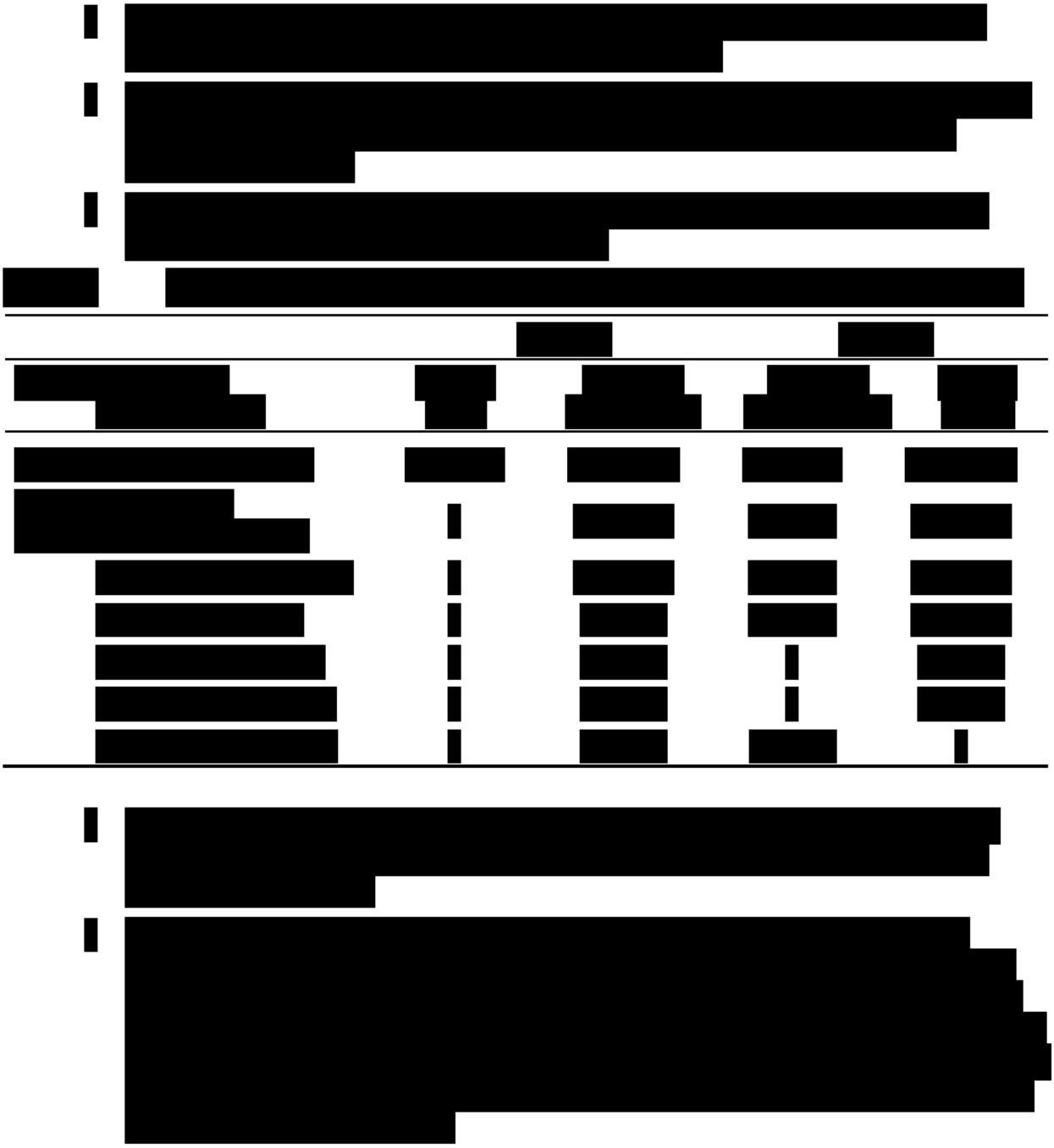
ARQ-151-101 (NCT03392168) was a Phase 2a study of two active doses of ARQ-151 cream, 0.5% and 0.15% vs vehicle in the topical treatment of adult subjects with chronic plaque psoriasis of up to 5% BSA involvement.

An initial cohort (Cohort 1) of 8 adult psoriasis subjects was treated with a single dose application of ARQ-151 cream 0.5% to a 25 cm^2 area of psoriatic plaque on the trunk or extremities (not on the face, genital area, palms or soles. Local tolerability and systemic safety labs were monitored. PK assessments were made at baseline (pre-dose), 1, 2, 4, 6 and 24 hours. Skin permeation of topically applied drug was ~0.4%. Local tolerability and systemic safety labs were unremarkable. Six Cohort 1 subjects plus 83 additional psoriasis subjects were then enrolled into Cohort 2, an inter-individual, parallel group, randomized and blinded assessment of

two concentrations of ARQ-151 drug product (0.15% and 0.5%) versus vehicle applied QD x 28 days, analyzing target psoriatic plaques for efficacy. Subjects were randomized 1:1:1 to receive 0.5% drug product, 0.15% drug product or vehicle to psoriatic plaques up to 5.0% of BSA. In each subject, up to 3 target plaques were identified for efficacy analysis.

PK assessments conducted on Day 1: 1, 2, 4 and 6 hours; Day 14: pre-dose (trough) and 1-hour post-dose; and Day 28: pre-dose (trough), 1, 2, 4, 6 and 24 hours.

Safety results follow:



[redacted]

Day 28 pharmacokinetic results of ARQ-151-101 are as follows:

[redacted]

2.3.1.2. Psoriasis Phase 2b (ARQ-151-201)

ARQ-151-201 (NCT03638258) was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.15%, ARQ-151 cream 0.3%, or vehicle cream was applied QD for 12 weeks to over 300 adult subjects with 2% to 20% BSA of chronic plaque psoriasis and baseline IGA of Mild or greater. In this study, both ARQ-151 cream 0.3% and ARQ-151 cream 0.15% were safe and well tolerated, demonstrating similar safety and tolerability profiles compared to each other and compared to vehicle. The safety data are summarized below:

[redacted]

[redacted]

Pharmacokinetic results of ARQ-151-201 are as follows:

[redacted]

2.3.1.3. Atopic Dermatitis Phase 1 PK Study in Adults (ARQ-151-102)

ARQ-151-102 was an open label, Phase 1, pharmacokinetics and safety study of ARQ-151 cream 0.15% and ARQ-151 cream 0.05% administered QD in adult subjects with mild to moderate AD.

[redacted]

2.3.1.4. Phase 1 Study in Adolescents and Pediatrics (ARQ-151-105)

ARQ-151-105 (NCT04156191) is an ongoing open-label, Phase 1, pharmacokinetics, maximal usage PK, safety, and efficacy study of ARQ-151 cream 0.15% administered QD in adolescent and pediatric subjects with mild to moderate atopic dermatitis.

The study is being conducted in three parts, the first two of which are completed. The first part consisted of three cohorts in which subjects aged 2 to 17 years old had 1.5 - 35% BSA involvement (excluding the scalp, palms, soles) and mild or moderate atopic dermatitis based on vIGA-AD.

The second part of the study consisted of three cohorts in which subjects were evaluated under maximal use conditions (MUSE) and had BSA involvement (excluding the scalp, palms, soles) of ≥35% in subjects 2 to 11 years old (inclusive) or ≥25% in subjects 12 to <17 years old with mild or moderate atopic dermatitis based on vIGA-AD. At least 60% of the enrolled subjects had moderate atopic dermatitis.

The third part of the study consists of one cohort (Cohort 7) in which subjects 2 to 5 years of age (inclusive) will be administered a lower concentration of ARQ-151 cream (0.05%) and evaluated under maximal use conditions (MUSE). Subjects will have BSA involvement (excluding the scalp, palms, soles) of ≥35% with mild or moderate atopic dermatitis based on vIGA-AD. At least 60% of the enrolled subjects will have moderate atopic dermatitis. This cohort of the study is ongoing.

Preliminary Study Results

[redacted]

2.3.1.5. Atopic Dermatitis Phase 2 Dose Ranging Study (ARQ-151-212)

ARQ-151-212 (NCT03916081) was a parallel group, double blind, vehicle-controlled, Phase 2 study that evaluated ARQ-151 cream 0.05% and 0.15% in the treatment of mild to moderate atopic dermatitis in 136 adolescent and adult subjects with 1.5 to 35% BSA of involvement.

Ninety-three female (68.4%) and 43 male (31.6%) subjects with mild to moderate AD participated in the study. Overall, the demographic and baseline disease characteristics were similar across all study groups. The mean age for all 136 study subjects was 41.6 years, including 8 adolescent subjects (between 12-17 years). The mean EASI score at Baseline for all study subjects was 9.04. The majority of subjects were in the moderate vIGA-AD category (77.9%). The mean BSA involvement was 9.5% for all study subjects.

[redacted]

2.3.2. Oral Roflumilast Tablet

Oral roflumilast (DALIRESP®) has been approved globally for the treatment of COPD and has been evaluated in nine Phase III/IV randomized double-blind clinical trials (Wedzicha 2016). Overall, the safety of oral roflumilast has been well established in its targeted population of mostly middle- and upper-aged individuals who currently smoke cigarettes or have smoked them extensively in the past. Adverse events (AEs) reported with roflumilast tablets have been consistent with those expected for oral PDE-4 inhibitors. In a pooled analysis of safety data from 6-month and 1-year clinical trials (N=8630), the most common AEs were diarrhea, weight loss and nausea. Other AEs reported more frequently with roflumilast treatment than with placebo were back pain, influenza, insomnia and decreased appetite (Michalski 2012; Wedzicha 2016).

In addition to the self-reported cases of weight loss in the 6-month and 1-year oral trials, clinically significant weight loss was also reported in two prospective studies that evaluated weight (Michalski 2012).

Psychiatric-related AEs were also greater in patients treated with roflumilast tablets (5.9%) compared to those treated with placebo (3.3%). The most common psychiatric-related AEs were insomnia, depression and anxiety. A small number of cases of completed suicide and suicide ideation have been reported in patients taking oral roflumilast in clinicals trials and also during post-marketing experience (Michalski 2012).

The only contraindication to oral roflumilast is use in patients with moderate to severe liver impairment (Child-Pugh B or C), where systemic levels of roflumilast may become elevated.

2.4. Rationale for Development

Atopic dermatitis is currently treated with topical calcineurin inhibitors and/or topical corticosteroids in combination with emollients. In 2016, Eucrisa® (crisaborole), a less potent PDE-4 inhibitor than roflumilast, was approved for the topical treatment of atopic dermatitis. Topical calcineurin inhibitors block the activation of T-lymphocytes and diminish inflammation, but are accompanied by a 'black box' warning for the development of lymphomas and other

lymphoproliferative diseases. Topical corticosteroids can cause skin atrophy and hypothalamic-pituitary axis suppression, and their use is often accompanied by poor adherence due to corticophobia (fear of using corticosteroids in patients or doctors). Eucrisa provides precedence for the effectiveness of topical PDE-4 inhibitors in atopic dermatitis, but it is a twice-daily ointment, its efficacy is modest, and its use is often accompanied by burning, stinging, and local skin reactions. In our Phase 2 AD study (ARQ-151-212), we observed excellent local toleration of ARQ-151 cream formulations. Since roflumilast is a more potent PDE-4 inhibitor than crisaborole (Hatzelmann 2010), ARQ-151 cream has potential to provide greater efficacy with better local toleration than Eucrisa.

This study will evaluate the long-term safety and efficacy of ARQ-151 cream in children, adolescent, and adult subjects with mild to moderate atopic dermatitis.

2.4.1. Dose Selection

The doses included in this study are the same as those included in the base studies (ARQ-151-311, ARQ-151-312 and ARQ-151-315) in which the subjects initiated treatment. Subjects 6 years and older will be treated with ARQ-151 cream 0.15%, and subjects 2 to 5 years old will be treated with ARQ-151 cream 0.05%. The selection of these doses in the prior studies is supported by data from ARQ-151-212 and ARQ-151-105.

In ARQ-151-212 (conducted in adult and adolescent subjects), results for the primary efficacy endpoint, mean absolute change from baseline in EASI score at Week 4, were numerically higher in the ARQ-151 cream 0.05% and ARQ-151 cream 0.15% ($p= 0.097$) groups than in the vehicle group. Furthermore, the result of the sensitivity analysis of the primary endpoint at Week 4 was statistically significant (ARQ-151 cream 0.15%, $p= 0.027$). Statistical significance was reached for numerous other clinically important efficacy endpoints including percent change from baseline in EASI score, EASI-75 responders, and subjects achieving vIGA-AD score of clear or almost clear. Both doses of topical roflumilast (0.15% and 0.05%) had a similar and favorable safety and tolerability profile, with generally more favorable efficacy observed at the ARQ-151 cream 0.15% dose. Results of this study support the use of ARQ-151 cream 0.15% in further studies of adult and adolescent subjects with mild to moderate AD. [redacted]

2.4.2. Risks and/or Benefits to Subjects

A favorable local and systemic benefit-risk profile has been observed in prior studies of ARQ-151 cream. Subjects 2 years of age and older enrolled in this study, may see an improvement in their atopic dermatitis with ARQ-151 cream 0.15% or ARQ-151 cream 0.05%, based on the activity of doses tested in atopic dermatitis (0.05% and 0.15%) and psoriasis (0.15% - 0.5%), and approval of a less potent topical PDE-4 inhibitor (crisaborole) for atopic dermatitis. Subjects may also see some benefit of ARQ-151 cream based on a potentially moisturizing effect of the formulation.

Oral roflumilast has been used for almost a decade in the treatment of COPD exacerbations and its safety profile is well-documented. The known adverse effects of oral treatment in the COPD population (nausea, vomiting, diarrhea, weight loss, psychiatric AEs (see Section 2.3.2) can be readily monitored as specified in this protocol. The profile that is emerging from studies of topical roflumilast appears different from the safety and tolerability profile of oral roflumilast. While oral PDE-4 inhibitors (DALIRESP, OTEZLA) have been associated with, in particular, a moderate incidence of GI AEs, these AEs, and perhaps others, appear to be reported far less frequently with topical PDE-4 inhibitors, including EUCRISA®, and ARQ-151 cream to date in clinical trials. For ARQ-151 cream, this may be related to the lack of 'peak to trough' C_{max} variation, lower C_{max} values than observed following oral administration, or bypassing of the gastrointestinal tract with topical administration.

This study has been designed with adequate safety monitoring practices (i.e., physical examinations, vital signs/weight, local skin toleration assessments, hematology, serum chemistry, urinalysis, PHQ-A/PHQ-8, CDI-2, C-SSRS and AE reporting). In addition, parents/caregivers of subjects 2 to 5 years of age will be advised to promptly report any changes in behavior that could signal psychological distress or emotional distress.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To assess long-term safety in a multicenter, open-label, single-arm study in subjects with atopic dermatitis treated with ARQ-151 cream 0.15% QD (subjects ≥6 years of age) or ARQ-151 cream 0.05% QD (subjects 2 to 5 years of age) after completing one of three Phase 3 studies (ARQ-151-311 or ARQ-151-312 or ARQ-151-315).

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary safety endpoints of this study are:

- Adverse Events
- Serious Adverse Events (SAEs)

3.2.2. Secondary Endpoints

The secondary endpoints of this study are:

- Validated Investigator Global Assessment-Atopic Dermatitis (vIGA-AD) value 0 or 1 at each assessment
- vIGA-AD success (defined as vIGA-AD value of 0 or 1 plus a 2-grade improvement from baseline)

- WI-NRS score over time
- EASI score over time

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3, open-label, single-arm, long-term safety study in which ARQ-151 cream 0.15% or ARQ-151 cream 0.05% is applied QD x 24 (Cohort-Week 24) or 52 weeks to subjects with mild to moderate atopic dermatitis (except for time on BIW maintenance therapy).

- Eligible subjects will enroll into the long-term safety study on the same day as the Week 4 visit of the preceding study (ARQ-151-311 or ARQ-151-312 or ARQ-151-315).
- Subjects/caregivers will apply ARQ-151 cream 0.15% for subjects ≥ 6 years old or ARQ-151 cream 0.05% for subjects 2-5 years old.
- If a 5 year-old subject turns 6 years-old during this study, the subject will be switched from ARQ-151 cream 0.05% to ARQ-151 cream 0.15% at his/her first scheduled post-birthday visit. Dose reduction back to 0.05% is not permitted.
- The study drug will be applied QD for 24 (Cohort-Week 24) or 52 weeks to all AD affected areas and any newly appearing AD lesions that arise during the study, except on the scalp (unless entering BIW maintenance therapy, as described below).
- **For the first 4 weeks of study ARQ-151-313, all subjects will apply study medication QD in the areas identified and treated as per the body diagram in the preceding study (ARQ-151-311/312/315).** Beginning at the Week 4 visit, any subject who achieves vIGA-AD of '0-clear' as confirmed by the Investigator at a scheduled or unscheduled clinic visit, will switch to twice weekly (BIW) maintenance treatment. For maintenance therapy, study medication will be applied on two nonconsecutive days per week (e.g. Monday and Thursday) to areas commonly and/or most recently affected by AD, and any areas where AD is developing. Subjects receiving maintenance treatment who experience AD worsening (signs and symptoms) for 1 week despite dosing twice weekly will phone the clinical study site, resume daily dosing, and complete the subject diary accordingly. The phone call (but not a clinic visit) is required to resume daily dosing. At clinic visits, subjects receiving maintenance treatment may continue twice weekly maintenance dosing if vIGA-AD is either '0-clear' or '1-almost clear'. Subjects will resume daily dosing if vIGA-AD ≥2, and can resume daily dosing if signs/symptoms of AD are not adequately controlled with maintenance therapy despite vIGA-AD of '1-almost clear'.

4.2. Number of Study Sites and Subjects

A total of up to approximately 1500 subjects will be enrolled at up to approximately 120 study sites in the United States and Canada. During the conduct of the study, additional countries and/or sites may be added if necessary. Subjects will be males and females 2 years and older. Only subjects 18 years and older will be enrolled at sites located in the province of Québec in Canada. Periodic clinic visits will include assessments for clinical safety, application site reactions, and disease improvement or progression.

4.3. Subject Participation

Subject participation involves a minimum of five clinic visits at Week 4, Week 12, Week 24, Week 36 and Week 52 of treatment. There will be three phone visits conducted at Weeks 18, 30 and 44. (For Cohort-Week 24, subject participation involves a minimum of three clinic visits at Week 4, Week 12 and Week 24 of treatment. There will be one phone visit conducted at Week 18). The Day 1 visit of this study will be Week 4 of the ARQ-151-311 or ARQ-151-312 or ARQ-151-315 study. The baseline value for safety and efficacy will be the last observation prior to the first dose of ARQ-151 cream in either the ARQ-151 preceding study (ARQ-151-311 or ARQ-151-312 or ARQ-151-315), or this study. The anticipated maximum duration of subject participation is about 24 or 52 weeks. Subjects in the ARQ-151-311 or ARQ-151-312 or ARQ-151-315 study that choose to participate in the long-term extension study will transition directly into the ARQ-151-313 study at the Day 1 visit (Week 4 of Study ARQ-151-311 or ARQ-151-312 or ARQ-151-315).

4.4. Numbering of Subjects

All subjects enrolled will retain their unique six-digit subject ID number previously assigned during the ARQ-151-311 or ARQ-151-312 or ARQ-151-315 study.

The study site is responsible for maintaining a current log of subject ID number assigned to each subject. The subject ID number will be used to identify the subject throughout the study and is required to be entered on all clinical study documentation (e.g., case report forms, labeling of clinical materials and sample containers, investigational product accountability logs, etc.).

4.5. Selection of Study Population

4.5.1. Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. For adult subjects: Participants legally competent to sign and give informed consent. For pediatric and adolescent subjects: Informed consent of parent(s) or legal guardian, and, if age appropriate, assent by the subjects, as required by local laws.
2. Males and females, ages 2 years and older. (Only subjects 18 years and older will be enrolled at sites located in the province of Québec in Canada.)

3. Subjects with atopic dermatitis who met eligibility criteria for and successfully completed ARQ-151-311 or ARQ-151-312 or ARQ-151-315 through Week 4, and are able and eligible to enroll into this long-term safety study on the Week 4 visit of the preceding study.
4. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at all study visits. In addition, sexually active FOCBP must agree to use at least one form of a highly effective or barrier method of contraception throughout the trial. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active.
5. Females of non-childbearing potential should either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status would have been confirmed with FSH testing in the preceding study) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
6. Subjects and parent(s)/legal guardian(s) are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

4.5.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from participation in this study:

1. Subjects who experienced a treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-151 cream in studies ARQ-151-311 or ARQ-151-312 or ARQ-151-315.
2. Subjects that use any Excluded Medications and Treatments (see Table 2).
3. Subjects with skin conditions other than AD that would interfere with evaluations of the effect of the study medication on AD, as determined by the Investigator. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements (e.g., molluscum contagiosum).
4. Subjects with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.
5. Known allergies to excipients in ARQ-151 cream [redacted]
6. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin during the study period.
7. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin during the study period.

8. Known or suspected:
   a. Severe renal insufficiency (defined as calculated creatinine clearance < 30mL/min)

   Refer to the creatinine levels from the following visits:

   - ARQ-151-311/ARQ-151-312 studies: Screening Visit for subjects ages 6-11 and Baseline/Day 1 for subjects ≥12 years old (for subjects 12-18 years old, if screening lab tests were collected within 3 weeks of Baseline/Day 1, screening results will be used)
   - ARQ-151-315 study: Screening Visit

   b. moderate to severe hepatic disorders (Child-Pugh B or C)
   c. history of severe depression, suicidal ideation or behavior
9. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
10. Subjects with any known serious medical condition (e.g., uncontrolled hypo- or hyper-thyroidism) or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
11. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication.
12. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
13. Subjects and parent(s)/legal guardian(s) who are unable to communicate, read or understand the local language(s), or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.
14. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects (subjects enrolled in other studies of ARQ-151 cream) living in the same house.

4.6. Study Restrictions

4.6.1. Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 2 (Excluded Medications and Treatments).

Generally, the addition of new medications, including nonprescription medications, during the course of the study is discouraged. However, the short-term use of a medication may be authorized by the Investigator. The Investigator must make the decision to authorize the use of any such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the medication will compromise the outcome or validity of the clinical investigation. Other medications may be authorized by the Investigator for conditions other than AD. If medication is required, the name,

strength, frequency, duration of use, and reason for use will be recorded in source documents and entered into the CRFs. Medications which have been used chronically by subjects, in particular statins and anti-hypertensives, are allowed for use during the study, except as prohibited in Table 2.

Non-medicated emollients, moisturizers and sunscreens can be applied to non-lesional and lesional skin. Subjects should maintain a stable moisturizer regimen and minimize changes to their moisturizer regimens and usual sunscreens.

Table 2: Excluded Medications and Treatments

Excluded Medications and Treatments
Biologics including dupilumab and investigational biologics
Systemic treatments that could affect AD; e.g. corticosteroids, retinoids, calcineurin inhibitors, hydroxycarbamide (hydroxyurea), methotrexate, cyclosporine, azathioprine, hydroxychloroquine, mycophenolate mofetil, or other immunosuppressive therapies.
PUVA or NBUVB phototherapy, tanning beds, other light emitting devices
Topical corticosteroids, calcineurin inhibitors, or Eucrisa®
Strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin
Strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine
Systemic antibiotics, except short courses, e.g., ≤15 days
Oral roflumilast (Daxas®, Daliresp®)
All other investigational drugs

Note:

- No rescue therapy is permitted per protocol.
- Eye / ear drop and nasal corticosteroid preparations are allowed. Inhaled corticosteroid preparations are allowed if used for a stable condition and at a stable dose.
- Non-medicated emollients, moisturizers and sunscreens can be applied to non-lesional and lesional skin. Subjects should maintain a stable moisturizer regimen and minimize changes to their moisturizer regimens and usual sunscreens.
- Concomitant other medications for chronic conditions (eg, NSAIDs, statins, anti-hypertensives) are permitted unless specifically prohibited in the Protocol.
- Topical antibiotics, topical antihistamines, or any other topical agents are not allowed to be applied to treated areas.

4.7. Treatment

4.7.1. IP Supplies, Packaging and Labeling

ARQ-151 cream will be supplied in 45 or 60 gram tubes. The tubes will be packaged in kits, containing multiple tubes of investigational product. The kit(s) dispensed to a subject will be labeled with a unique number.

The Sponsor will supply sufficient quantities of the study drug to each study site to allow for completion of this study.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any used/unused study drugs will be returned to the Sponsor or designee, or destroyed, as per Sponsor instructions.

Refer to the most current version of the IP Handling Plan for details on accountability, storage, and management of ARQ-151 cream.

4.7.2. Blinding

This is an open label study, therefore the subjects, the Investigator, clinical personnel, and the sponsor will be aware of which treatment an individual subject receives.

4.7.3. Treatment Administration

Initial treatment with the IP in the ARQ-151-313 will occur on Day 1 (Day 29 from the preceding study). ARQ-151 cream 0.15% or ARQ-151 cream 0.05% is administered once daily (unless entering BIW maintenance therapy) as a topical product to cover the skin surface at an application rate of approximately 2 mg/cm^2.

At Day 1 visit, the study staff will redemonstrate to the subject/caregiver(s) how to apply ARQ-151 cream using the first tube from the kit that is assigned to the subject. Study site staff will be retrained to ensure a unit dose (a pea size unit of ARQ-151 cream will cover approximately 1% BSA) is properly squeezed from the tube and applied to atopic dermatitis lesion(s) as a thin film and rubbed in using the index and middle finger, rubbing in thoroughly but gently, until the 'white' has disappeared. The subject/caregiver will then practice squeezing a similar amount onto their index and middle finger and apply a thin film to other areas to be treated. At Day 1, the study staff will ensure that the subject/caregiver's application technique is correct and that a thin layer is applied as instructed (which represents an application rate of approximately 2 mg/cm^2).

Re-training will be conducted at subsequent visits as needed (i.e., if the returned tube(s) weighs substantially different than the expected weight).

For the first 4 weeks of study ARQ-151-313, all subjects will apply study medication QD in the areas identified and treated as per the body diagram in the preceding study (ARQ-151-311/ 312/315). Beginning at the Week 4 visit, any subject who achieves vIGA-AD of '0-clear' as confirmed by the Investigator at a scheduled or unscheduled clinic visit, will switch to twice weekly (BIW) maintenance treatment. For maintenance therapy, study medication will be applied on two nonconsecutive days per week (e.g. Monday and Thursday) to areas commonly

and/or most recently affected by AD, and any areas where AD is developing. Subjects receiving maintenance treatment who experience AD worsening (signs and symptoms) for 1 week despite dosing twice weekly will phone the clinical study site, resume daily dosing, and complete the subject diary accordingly. The phone call (but not a clinic visit) is required to resume daily dosing. At clinic visits, subjects receiving maintenance treatment may continue twice weekly maintenance dosing if vIGA-AD is either '0-clear' or '1-almost clear'. Subjects will resume daily dosing if vIGA-AD ≥2, and can resume daily dosing if signs/symptoms of AD are not adequately controlled with maintenance therapy despite vIGA-AD of '1-almost clear'.

Note:

- For daily dosing from Week 4 onwards, study medication should be applied to any areas where AD is active or developing, and areas commonly and/or most recently affected by AD.
- All subjects should apply medication each evening (unless on BIW maintenance therapy) except on Day 1 when medication application will be done on site. If the subject takes an evening shower/bath, the ARQ-151 cream can be applied as soon as the skin is nearly dry, but no later than 20 minutes before going to bed. Subjects are not to wash areas where ARQ-151 cream has been applied until at least 2 hours after study drug application.
- Caregivers should wash their hands with soap and water after applying IP to a child.
- Parents/guardians/caregivers who are pregnant, or women of childbearing potential who are trying to become pregnant, or who are breastfeeding, or planning to breastfeed during the study should avoid accidental exposure by either avoiding applying investigational product or by wearing gloves during its application.
- New lesions that develop during the study should be treated (except scalp). An unscheduled visit is not required for starting treatment of new lesions.

Each investigational product tube will be weighed prior to dispensing at the Day 1 visit and at each subsequent visit. Investigational product tubes must be returned by subjects at each study visit, both empty and full, and will be weighed. If the subject's actual use is substantially different than the expected use for the subject's BSA (see IP Handling Plan), the subject/caregiver will be retrained on the study drug application technique.

4.7.4. Treatment Compliance

Investigational product tubes will be weighed at each clinic visit.

Subjects/caregivers will complete a daily diary recording the date and time of each dose applied, any missed doses, and a comment section should the subjects have a comment, e.g., record potential AEs. Study site personnel will review the diaries and use the information to question the subject regarding compliance and AEs and then record appropriate information in source documents and complete Case Report Forms (CRFs). If a subject misses a dose, they should be instructed to return to the protocol investigational product administration schedule (i.e. if subject forgets a dose they should wait until that evening and apply as usual).

A subject will be considered compliant with the dosing regimen if the subject meets both of the following requirements:

- applies at least 80% of the expected applications during the study drug application period
- does not miss more than 3 consecutive doses

Compliance will be assessed by review of the dosing diary. Weight of investigational product applied (via dispensed and returned tube weights) will be measured.

If the diary shows less than 80% of expected applications (but not more than 3 consecutive missed doses), the subject is using too little study drug and retraining must be conducted and documented.

Compliance will be documented in source and in eCRF.

4.7.5. Removal of Subjects from Study Treatment

A subject may discontinue study treatment for any of the following reasons:

1. Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements for investigational product as per the Protocol.
2. Adverse Events as described in Section 5.9 the Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
3. Treatment must be discontinued immediately in the event of a female subject's pregnancy.
4. Subject's decision to discontinue treatment with study drug.
5. C-SSRS (Section 5.1.10) indicative of suicidal ideation (score > 0).
6. PHQ-8 (Section 5.1.7) or modified PHQ-A (Section 5.1.8) score ≥15 if determined by Investigator in consultation with mental health professional.
7. CDI-2 (Section 5.1.9) raw total score of ≥32 if determined by Investigator in consultation with mental health professional.

4.7.6. Removal of Subjects from the Study

A subject may be removed from study participation for any of the following reasons:

1. Subject death.
2. Subject's decision to withdraw from study.
3. Subject is lost to follow-up. A subject will be considered lost to follow-up after three phone and three email attempts and documentation of a certified letter sent to the subject's address.

4. Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
5. Subject's repeated failure to comply with protocol requirements or study related procedures.
6. The subject interrupts trial study drug application for more than 50% of scheduled doses.
7. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

5. STUDY PROCEDURES

The Schedule of Visits and Assessments (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below.

5.1. Safety Assessments

This study assesses the long-term safety and efficacy of ARQ-151 cream. Safety will be determined by evaluating physical examinations, local tolerability assessments, vital signs/weight, clinical laboratory parameters (subjects ≥12 years old), either PHQ-8 (adults, ≥18 years old) or modified PHQ-A (adolescents, 12-17 years old) or Children's Depression Inventory 2 (CDI-2, parent report for children 6-11 years old, inclusive), C-SSRS (12 years and older) and AEs as outlined in the Schedule of Visits and Assessments (Section 1.3).

Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

5.1.1. Day 1 Visit

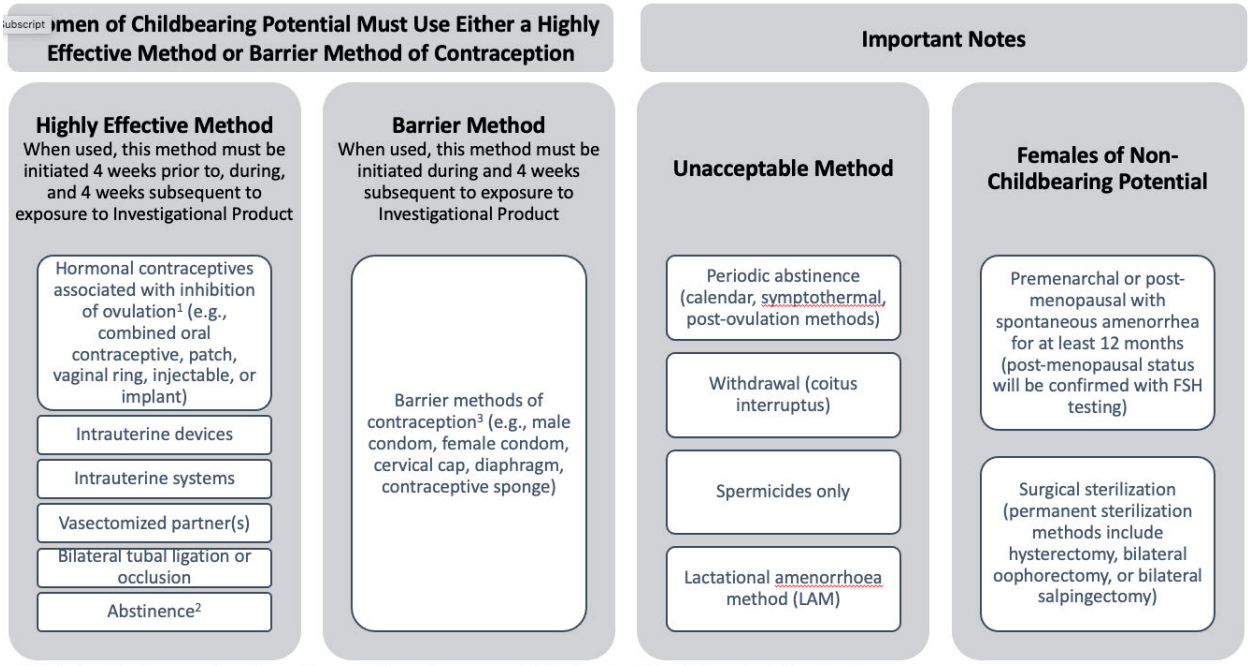
At Day 1 (Week 4 of the ARQ-151-311 or ARQ-151-312 or ARQ-151-315 study) subjects from these preceding studies will be provided details of study requirements and sign an informed consent. Subjects will continue with the safety and efficacy assessments specific to their age group at the time of consent/assent at Screening of the preceding study. Medical and surgical history collected in the preceding study will be used in the ARQ-151-313 study. Only new information and updates will need to be collected at Day 1 visit. Atopic dermatitis assessments (vIGA-AD, BSA, EASI, SCORAD), physical examination, vital sign measurements (blood pressure, heart rate, and temperature), WI-NRS, CDI-2, DLQI, CDLQI, IDQOL, DFI, C-SSRS, POEM, and PHQ (-8 or -A), medical photography, laboratory tests: hematology, chemistry, urinalysis and a pregnancy test for female subjects of child bearing potential will be obtained at Week 4 visit of ARQ-151-311 or ARQ-151-312 or ARQ-151-315 study and will serve as the Day 1 for ARQ-151-313 subjects. The baseline value for safety and efficacy will be the last observation prior to the first dose of ARQ-151 cream in either the ARQ-151 preceding study (ARQ-151-311 or ARQ-151-312 or ARQ-151-315), or this study.

All subjects will retain their Subject ID from the preceding study which will be entered into the electronic subject tracking system for this long-term safety study.

5.1.2. Contraception Requirements

Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at Day 1 of study ARQ-151-313. In addition, sexually active FOCBP must agree to use at least one form of a highly effective or barrier method of contraception throughout the trial according to Contraception Requirements (Figure 1).

Figure 1: Contraception Requirements for Female Subjects



[1]Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.
[2]The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
[3]Female condom and male condom should not be used together.

5.1.3. Day 1

Enrollment will take place at the Day 1 visit after the subject has been found to be fully eligible for participation. A subject will be considered enrolled into the study upon the first IP application.

5.1.4. Physical Examination

Physical examinations will be performed according to the Schedule of Visits and Assessments (Section 1.3). The physical exam will be limited to skin, lungs and heart only.

5.1.5. Vital Signs, Height and Weight

Vital signs will be performed according to the Schedule of Visits and Assessments (Section 1.3). Blood pressure, heart rate, and temperature will be collected in seated position after 5 mins of rest. For weight measurement, subjects will be instructed to void prior to weight being taken and to remove any objects of significant weight (i.e. jackets, outerwear, shoes, cell phones, wallet,

key chains, etc.). Weight should be obtained using a calibrated weight scale and the same scale, whenever possible, should be used for a subject throughout the duration of the study. The subject should stand with both feet in the center of the scale with their arms at their side and hold still. Record the weight to the nearest decimal fraction (for example, 25.1 kilograms) For subjects <18 years of age, measure the weight in triplicate and report the average weight in EDC. An unexplained, clinically significant weight loss should be reported to the Medical Monitor.

Height will be measured at every clinic visit for subjects <18 years old and at Day 1 only for subjects ≥18 years old.

5.1.6. Laboratory Tests

All tests listed in Table 3 below will be performed according to the Schedule of Visits and Assessments (Section 1.3) unless otherwise noted. No food restrictions are required for the collection of specimens. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Table 3: Laboratory Tests

Hematology	**Serum Chemistry**
• Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count with indices and morphology • Platelet count	• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Chloride • Glucose • Creatinine
Urinalysis*	**Additional Tests**
• pH • Specific gravity • Protein** • Glucose • Ketones • Bilirubin • Blood** • Nitrite** • Urobilinogen • Leukocyte esterase**	• Urine pregnancy test*** (for females of child bearing potential only)

* Hematology, Serum Chemistries, and Urinalysis is only done in subjects ≥ 12 years of age (unless needed by an investigator to evaluate an adverse event).

** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

*** At Day 1 and Weeks 4, 12, 24, 36, and 52 for FOCBP only (If subject is enrolled into Cohort-Week 24, at Day 1 and Weeks 4, 12, and 24 only).

5.1.7. Patient Health Questionnaire Depression Scale (PHQ-8)

The PHQ-8 Assessment (Appendix 1) will be performed in adult subjects according to the Schedule of Visits and Assessments (Section 1.3).

PHQ-8 score is the sum of the responses for the 8 questions.

Five severity categories of depression are defined as follows:

- None – Minimal depression (0 to 4)
- Mild depression (5 to 9)
- Moderate depression (10 to 14)
- Moderately severe depression (15 to 19)
- Severe depression (20 to 24)

A subject with a PHQ-8 score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score.

A subject with a PHQ-8 score ≥15 should be immediately referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the study drug.

5.1.8. Patient Health Questionnaire Depression Scale (Modified PHQ-A)

The Modified PHQ-A Assessment (Appendix 2) will be performed in adolescent subjects (12-17 years old, inclusive).

Modified PHQ-A score is the sum of the responses for five severity categories of depression defined as follows:

- None – Minimal depression (0 to 4)
- Mild depression (5 to 9)
- Moderate depression (10 to 14)
- Moderately severe depression (15 to 19)
- Severe depression (20 to 24)

A subject with a modified PHQ-A score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score.

A subject with a modified PHQ-A score ≥15 should be immediately referred to a mental health professional, and the Investigator in consultation with the mental health professional should consider interruption or discontinuation of the study drug.

5.1.9. Children's Depression Inventory 2 (CDI-2)

The CDI-2 Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3) for subjects 6 to 11 years old, inclusive.

The CDI-2 quantifies depressive symptomatology using reports from children/adolescents, teachers, and parents or caregivers. It is recommended for use in initial evaluation and is appropriate when there is a need for an assessment and robust description of a child's depressive symptoms.

This study will use the CDI Parent Report Form. An example of the Parent report form is presented in Appendix 3.

A subject with a CDI-2 raw score of ≥21 for females and ≥22 for males should be referred to a mental health professional for evaluation.

A subject with a CDI-2 raw total score of ≥32 should be referred to a mental health professional, and the Investigator in consultation with the mental health professional should consider interruption or discontinuation of the study drug.

5.1.10. Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3) for subjects 12-years old and older.

The administration schedule of the C-SSRS will be:

- The "Since Last Visit" version (Appendix 4) will be used at all visits.
- A score greater than 0 at the Baseline visit in suicidal ideation may indicate the need for mental health intervention. The investigator should not enroll the subject in the study.
- Any score greater than 0 in the suicidal ideation score may indicate the need for mental health intervention. The Investigator should give consideration for the subject to discontinue from the study drug and prompt referral to an identified mental health professional and/or an appropriate emergency room. The Medical Monitor should be contacted.

The C-SSRS administer will be trained via the C-SSRS training video. A training certificate for the administer(s) will be on file in the trial master file at the study site.

The Investigator must review the completed C-SSRS. A qualified mental health care provider must be available, immediately if needed, to refer the subject for further evaluation.

5.1.11. Local Tolerability Assessment

The Investigator Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

At Day 1 only, local tolerability assessments should be recorded prior to study drug application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score).

Application site reactions will be graded at each timepoint. Irritation reactions are graded using the scale detailed in the following section (Berger 1982). **Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's atopic dermatitis.**

The investigator assessments will be conducted by the investigator or a properly trained and designated subinvestigator in the clinic.

Dermal Response

0. no evidence of irritation
1. minimal erythema, barely perceptible
2. definite erythema, readily visible; minimal edema or minimal papular response
3. erythema and papules
4. definite edema
5. erythema, edema and papules
6. vesicular eruption
7. strong reaction spreading beyond application site

Other Effects

A. = slight glazed appearance
B. = marked glazing
C. = glazing with peeling and cracking
D. = glazing with fissures
E. = film of dried serous exudates
F. = small petechial erosions and/or scabs
G. = no other effects

The Subject Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

At Day 1 only, local tolerability assessments should be recorded 10-15 minutes post-drug application for the Subject's '0-3' burning/stinging assessment.

The subject will assess burning/stinging (0-3 score), (For subjects <6 years of age, parents will complete.):

Grade	Sensation Following Drug Application
0 (none)	No sensation
1 (mild)	Slight warm, tingling sensation; not really bothersome
2 (moderate)	Definite warm, tingling sensation that is somewhat bothersome
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort

This assessment will be administered by the study site at Day 1 and at every clinic visit.

- **Note: for subject burning stinging assessment at every clinic visit after Day 1, subjects will provide a recall assessment of burning/stinging experienced at most recent dosing.**

5.1.12. Adverse Events

Adverse events (AEs) will be collected and assessed throughout the study according to the Schedule of Visits and Assessments (Section 1.3).The Investigator is responsible for ensuring that all adverse events observed by the clinical staff or reported by the subject that occur after the first application of investigational product through the end of the study are recorded in the subject's medical record and the eCRF.

The Investigator is responsible for ensuring that all serious adverse events observed by the clinical staff or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the application of the investigational product or the end of study (whichever is later) are recorded in the subject's medical record and are submitted per SAE reporting requirements (Section 5.7.5).

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up for up to 30 days after end of treatment or until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI. Refer Section 5.7 for further details on Adverse Events.

5.1.13. Phone Follow Up Visit

Phone Follow Up Visits will be conducted according to the Schedule of Visits and Assessments (Section 1.3) for all subjects to review any adverse event or concomitant medication changes.

5.2. Efficacy Evaluations

Palms and soles may be treated with investigational product in this study, but will not be counted towards vIGA-AD, EASI, or BSA assessments. EASI is evaluated for the entire body except the scalp, palms, and soles.

5.2.1. Validated Investigator Global Assessment scale for Atopic Dermatitis

Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) assessments should be completed prior to other physician assessments.

vIGA-AD assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3). The vIGA-AD is a static evaluation of qualitative overall AD severity. This global assessment scale is an ordinal scale with five severity grades (reported only in integers of 0 to 4). Each grade is defined by a distinct and clinically relevant morphologic description that minimizes inter-observer variability (see Appendix 5). vIGA-AD is evaluated for the entire body except the scalp, palms, and soles.

Note: All atopic dermatitis lesions on a subject will be treated including the face, trunk, genitals/skin folds, or limbs (excluding the scalp). The palms and soles will be treated but will not be counted towards any measurements of efficacy (EASI, vIGA-AD, BSA).

Every effort must be made for the same Evaluator to complete the IGA for the subject at every study visit.

IGA will be assessed at clinic visits.

5.2.2. Eczema Area and Severity Index (EASI)

EASI scores (Hanifin 2001) will be performed according to the Schedule of Visits and Assessments (Section 1.3)

Four anatomic sites—head, upper extremities, trunk, and lower extremities—are assessed for erythema, induration/infiltration (papules), excoriation, and lichenification as seen on the day of the examination. The severity of each sign is assessed using a 4-point scale (half steps **are** allowed; e.g. 0.5, 1.5 and 2.5):

0 = none
1 = mild
2 = moderate
3 = severe

The area affected by atopic dermatitis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of atopic dermatitis involvement as follows:

0 = no involvement
1 = 1-9%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

The EASI score is obtained by using the formula below for subjects ≥8 years old:

$$\text{EASI} = 0.1\,(E_h + I_h + Ex_h + L_h)\,A_h + 0.2\,(E_u + I_u + Ex_u + L_u)\,A_u + 0.3\,(E_t + I_t + Ex_t + L_t)\,A_t + 0.4\,(E_l + I_l + Ex_l + L_l)\,A_l$$

The EASI score is obtained by using the formula below for subjects <8 years old:

$$\text{EASI} = 0.2\,(E_h + I_h + Ex_h + L_h)\,A_h + 0.2\,(E_u + I_u + Ex_u + L_u)\,A_u + 0.3\,(E_t + I_t + Ex_t + L_t)\,A_t + 0.3\,(E_l + I_l + Ex_l + L_l)\,A_l$$

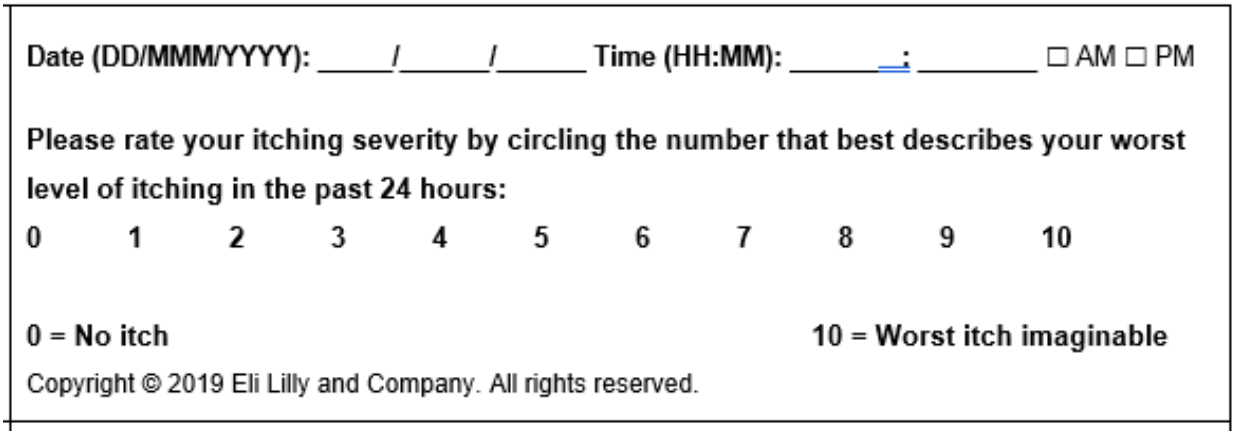
Where E, I, E*x*, L, and A denote erythema, induration, excoriation, lichenification and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

Note: Palms and soles may be treated with investigational product in this study, but will not be counted towards IGA, EASI, or BSA assessments. EASI is evaluated for the entire body except the scalp, palms, and soles.

Note: If a subject turns 8 years old during the study, the formula used at Screening of the preceding study will continue to be used through the duration of the subject's participation in this study.

5.2.3. Worst Itch Numerical Rating Scale (WI-NRS)

The WI-NRS has been developed as a simple, single item to assess the patient-reported severity of this symptom at its highest intensity during the previous 24-hour period. (Newton 2019). The WI-NRS will be determined once a week by the subject recording their worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst itch imaginable" or "worst imaginable itch").


Date (DD/MMM/YYYY): _____/_____/_____ Time (HH:MM): _____:_____ ☐ AM ☐ PM

Please rate your itching severity by circling the number that best describes your worst level of itching in the past 24 hours:

0 1 2 3 4 5 6 7 8 9 10

0 = No itch 10 = Worst itch imaginable

The WI-NRS will be **self-reported by subjects for subjects ≥ 6 years of age,** and reported by parent/guardian for subjects <6 years of age. Subjects and/or parent/guardians will be reminded not to review responses from the previous weeks when completing the WI-NRS. Parent and/or guardian will be trained at the baseline visit to assist the subject, if needed, in the accurate

completion of the WI-NRS. Caregiver/parents will be given instructions on how to complete this questionnaire for subjects between 2 and 5 years of age.

WI-NRS Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

5.2.4. Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)

The DLQI (ages 17+ years) and CDLQI (subjects ≥4 years of age and ≤16 years of age (based on age at start of preceding studies ARQ-151-311/312/315) will be performed according to the Schedule of Visits and Assessments (Section 1.3). Subjects who were assessed using CDLQI in their preceding study (ARQ-151-311/312/315) will remain on CDLQI in the current study (ARQ-151-313). The DLQI/CDLQI is a simple, self-administered and user-friendly validated questionnaire. The DLQI/CDLQI is designed to measure the health-related quality of life of adult patients suffering from a skin disease. The DLQI/CDLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. Subjects/caregivers will complete the CDLQI/DLQI. Refer to Appendix 6 for the DLQI and Appendix 7 for the CDLQI.

5.2.5. Infants' Dermatitis Quality of Life Index (IDQOL)

IDQOL (Appendix 8) will be performed according to the Schedule of Visits and Assessments (Section 1.3). The Infants' Dermatitis Quality of Life Index questionnaire is designed to assess the impact of atopic dermatitis on the quality of life of infants below the age of four years. Subjects who were assessed using IDQOL in their preceding study (ARQ-151-315) will remain on IDQOL in the current study (ARQ-151-313).

It should be completed by the child's parent(s) or regular caregiver.

5.2.6. Dermatitis Family Impact Questionnaire (DFI)

This questionnaire measures how much having a child with atopic dermatitis affects the quality of life of other (adult) members of the family. To be completed by parents/guardians/caregivers of subjects ≤17 years of age (Appendix 9). DFI is not to be conducted for subjects who were ≤17 years of age in the ARQ-151-311/312 studies and turned 18 years of age prior to enrollment into ARQ-151-313.

5.3. Other Evaluations

5.3.1. Body Surface Area (BSA)

BSA assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The BSA affected for atopic dermatitis will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of body surface area (excluding the scalp, palms, soles).

5.3.2. SCORAD ("SCORing Atopic Dermatitis")

SCORAD assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

SCORAD is a clinical tool for assessing the severity (i.e. extent, intensity) of atopic dermatitis as objectively as possible. It gives approximate weights of 60% to intensity and 20% each to spread (extent) and subjective signs (insomnia, etc.). SCORAD total score will range between 0 and 103.

See Appendix 10.

5.3.3. Patient-Oriented Eczema Measure (POEM)

POEM assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The Patient-Oriented Eczema Measure (POEM) is a tool used for monitoring atopic eczema severity. It focuses on the illness as experienced by the patient.

POEM is a 5-point scale measuring the frequency of each of seven AD symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) over the past week scored as occurring "no days" (0), "1 to 2 days" (1), "3 to 4 days" (2), "5 to 6 days" (3) or "every day" (4). Total score ranges from 0–28, with higher score indicating greater symptom impact. See Appendix 11. The self/proxy report questionnaire will be used in this study (for children unable to read and/or understand the POEM questionnaire, the parent/guardian/caregiver will complete the questionnaire).

5.3.4. Pharmacokinetics Assessment

PK draws will be performed according to the Schedule of Visits and Assessments (Section 1.3) for all subjects at all sites under this Amendment 1:

- A single PK assessment (trough) will be performed in subjects ≥12 years old with a blood sample collected at Week 52/ET.
- No PK sample will be collected at Week 52/ET for subjects 2-11 years old.

Ensure study medication is not applied in the area where PK will be drawn.

5.3.5. Medical Photography

Photography of AD lesion(s) selected by the Investigator will be performed by all study sites at all investigational visits, except Weeks 18, 30, and 44. All efforts will be made to de-identify the subjects. Canfield equipment will be used to capture photographs.

Photography should be focused on single lesions or specific body sections (e.g. arm). Body or half body photos should only be taken if necessary. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure and documented on the informed consent.

Refer to the current Photography Manual for instructions regarding photography.

5.4. Final Study Visit – End of Study

The approximate final study visit will occur at Week 52, except for subjects in the Cohort-Week 24, where the final study visit will occur at Week 24. The procedures performed during this visit are as described in the Schedule of Visits and Assessments (Section 1.3). A 7-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the participant or and followed to resolution or stabilization (as necessary).

5.5. Early Termination Visit

If a subject is withdrawn or wishes to exit the study, a termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 52 visit.

5.6. Unscheduled Visit

Beginning at the Week 4 visit, any subject who achieves vIGA-AD of '0-clear' as confirmed by the Investigator at a scheduled or unscheduled clinic visit, will switch to twice weekly (BIW) maintenance treatment. For maintenance therapy, study medication will be applied on two nonconsecutive days per week (e.g. Monday and Thursday) to areas commonly and/or most recently affected by AD, and any areas where AD is developing. Subjects receiving maintenance treatment who experience AD worsening (signs and symptoms) for 1 week despite dosing twice weekly will phone the clinical study site, resume daily dosing, and complete the subject diary accordingly. The phone call (but not a clinic visit) is required to resume daily dosing.

Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted in the judgement of the Investigator.

The following information will be collected for all subjects:

- Concomitant medications/procedures
- AEs

The following information also will be collected:

- vIGA-AD and EASI
- BSA affected with AD
- Local tolerability assessment (by Investigator)

However, if an unscheduled visit is required for reasons other than safety (e.g. procedures such as labs or images that were either missed at the regular subject visit or need to be repeated), the vIGA-AD and EASI, BSA affected with AD, and Local Tolerability assessment (by Investigator) are not required.

The rules for how to tally vIGA-AD, BSA or other proportions of categorical responses will be described in the Statistical Analysis Plan.

5.7. Adverse Events

5.7.1. Adverse Event Definition

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A treatment emergent adverse event (TEAE) is defined as an AE that started post application of study medication at the Day 1 visit of study ARQ-151-313 or was present at treatment initiation but worsened during treatment, through study completion.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (eg, worsening hypertension for a subject with pre-existing hypertension). A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Progression of atopic dermatitis including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

5.7.2. Serious Adverse Event Definition

The definitions and reporting requirements of the Food and Drug Administration (FDA)/ ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. Statements regarding mandatory reporting of all serious unexpected adverse drug reactions (SUSARs) to Health Canada [as per C.05.014 (1) of the FDR] will be adhered. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed.

An SAE is defined as any AE that, in the view of either the PI or Sponsor, meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity/disability
- Congenital anomaly/birth defect
- Other important medical events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g. caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

Unexpected is defined as an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or study document.

If a SAE occurs to a subject on this study, contact the Medical Monitor within one business day of knowledge of event.

5.7.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR is defined as a serious adverse reaction, the nature or severity of which is not consistent with the known study treatment information. A serious event or reaction is not defined as a SUSAR when: ‘it is serious but expected’ or it does not fit the definition of an SAE, whether expected or not.

5.7.4. Safety Review with Subject

At each subsequent clinic visit after the Day 1 visit, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?' Additionally, the study staff will review subject diaries and, if it appears that a potential AE was recorded, study staff will query the subject and determine if an AE occurred.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed for up to one month after end of treatment until the symptoms or value(s) return to normal, or acceptable levels, as judged by the Investigator.

Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

5.7.5. Adverse Event Reporting

The Investigator is responsible for recording all adverse events, observed by the clinic staff or reported by the subject that occur after the first application of investigational product in the ARQ-151-313 study through one month after treatment permanently discontinues. Serious adverse events observed by the clinic staff or reported by the subject after signing the informed consent form will be recorded.

All adverse events that meet the criteria for "serious" (i.e., SAEs) will be reported to the Sponsor via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. Reporting should be done by sending the completed SAE form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible).

Safety Contact Information: [redacted]

[redacted]

All serious event reporting will adhere to ICH E6: Guideline for Good Clinical Practice and ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. The IRB will be notified of the Alert Reports as per FDA, ICH and the IRB's policies and procedures. The sponsor, or delegate, will be responsible for reporting SAEs to health authorities per local reporting requirements. The Investigator will be responsible for reporting events to their respective IRBs in accordance to the IRB requirements.

The Investigator will review each adverse event and assess its relationship to Investigational Product (unrelated, unlikely, possibly, probably, likely). Each sign or symptom reported will be graded on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

- The relationship of each AE to the Investigational Product will be assessed using the following definitions:

Unrelated	The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. Definitely not related to drug. Temporal sequence of an AE onset relative to administration of drug not reasonable. Another obvious cause of an AE.
Unlikely	Time sequence is unreasonable. There is another more likely cause for an AE.
Possibly	Corresponds to what is known about the drug. Time sequence is reasonable. Could have been due to another equally, likely cause.
Probably	Is a known effect of the drug. Time sequence from taking drug is reasonable. Ceases on stopping the drug. Cannot be reasonably explained by the known characteristics of the subject's clinical state.
Likely	Is a known effect of the drug (e.g., listed in Physicians' Desk Reference, Compendium of Pharmaceuticals and Specialties, IB). Time sequence from taking drug is reasonable. Event stops upon stopping drug, event returns upon restarting drug.

The following CTCAE toxicity grading scale 5-point severity scale definitions for rating maximum severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.** Note: An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Note:

* A semi-colon indicates 'or' within the description of the grade.
* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AEs will be coded using the most current MedDRA® version available at the time of database lock.

5.8. Reporting Pregnancy

During study participation, all subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, Investigational Product must be discontinued immediately, the subject should be referred to an obstetrician experienced in reproductive toxicity for evaluation and counseling, and the subject should be followed until conclusion of the pregnancy.

The investigator is responsible for reporting all available pregnancy information on the pregnancy report and submitting to the Medical Monitor within 24 hours of becoming aware of the event, although pregnancy itself is not considered an AE. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available. Any pregnancy resulting in a congenital abnormality or birth defect of the newborn, or neonatal death occurring within 30 days of the birth must be reported as a SAE, regardless of causality. Any infant death that occurs after the 30 day reporting period that the investigator suspects is related to Investigational Product must also be reported as an SAE.

Partner pregnancies of a male subject do not need to be reported.

5.9. Treatment Stopping Rules

If a subject has non-cutaneous adverse events of concern, clinically significant laboratory values or any condition that the investigator determines could possibly be related to the study drug, the Investigator should immediately contact the Medical Monitor to discuss if the subject should be discontinued from treatment with investigational product.

Treatment for any individual subject will be discontinued if the subject experiences:

- A serious adverse event (SAE) or a clinically significant non-serious AE which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the study for that subject's well-being.
- A severe (Grade 3) laboratory abnormality (confirmed by repeat sample and considered related to study drug [Appendix 12]).

A subject with a PHQ-8 or modified PHQ-A score ≥15 should receive immediate referral to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the study drug.

A subject with a CDI-2 raw total score of ≥32 should be referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the study drug.

A subject 2 to 5 years of age that is exhibiting behavioral changes that may signal psychological or emotional distress should be evaluated immediately by the investigator to determine if referral to a qualified mental health care provider is necessary, and consideration should be given to discontinuing study drug.

A subject that is experiencing suicidal ideation and behavior should be referred immediately to a qualified mental health care provider and consideration given to discontinuation from study drug.

As noted above, study treatment must be discontinued immediately in the event of a female subject's pregnancy.

Treatment should be interrupted:

- If a subject develops an application site reaction with the clinical appearance of an 'irritation reaction', and with a severity of a Dermal Response Score of 5 (erythema, edema and papules) or greater on the scale of Berger and Bowman, treatment should be interrupted for up to one week and may then be resumed if the reaction has, in the opinion of the Investigator, adequately resolved.

Treatment should be discontinued:

- If the application site reaction reoccurs, treatment should be discontinued permanently, and the subject followed until the reaction resolves.

For cases of suspected allergic contact dermatitis, the medical monitor and sponsor should be notified and there should be discussion about performing patch testing to further evaluate. Patch testing is encouraged in such cases.

6. DATA ANALYSIS

Data will be handled and processed according to the Contract Research Organization's Standard Operating Procedures, which are written based on the principles of GCP.

Full details of the statistical analysis will be included in the Statistical Analysis Plan (SAP).

Data from this study may be analyzed prior to the final analysis for regulatory reporting purposes. Under Amendment 1, subjects 6-17 years of age that have completed the 4-week treatment period in ARQ-151-311 or ARQ-151-312 will be treated for 24 weeks with ARQ-151 cream 0.15% (Cohort-Week 24). The rest of the subjects will be treated for up to 52 weeks with ARQ-151. The analysis will be performed by cohorts and overall over time.

6.1. Statistical Methods

The methodology presented below is a summary of the more detailed analysis plan that will be presented in the Statistical Analysis Plan (SAP). The SAP will be finalized before the database is locked. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

All statistical processing will be performed using SAS® (Version 9.4) unless otherwise stated.

6.2. Determination of Sample Size

There are approximately 1500 subjects planned for this study.

The sample size will provide a sufficient number of subjects to evaluate the long-term safety of ARQ-151 cream 0.15% or ARQ-151 cream 0.05% over 24 or 52 weeks of treatment, and in combination with other studies provide the development program with sufficient numbers of subjects to meet ICH exposure goals.

6.3. Subjects to Analyze

The safety populations are defined as all subjects who are enrolled and received at least one confirmed dose of study medication.

Pharmacokinetic Population (PK): The PK population includes all subjects receiving

active drug and had a PK draw (concentration data available) post-baseline. This population will be used for the analysis of PK concentrations.

6.4. Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and background characteristics for the enrolled subjects.

6.5. Study Medication Compliance

The number of study drug applications by each subject based on diary data will be summarized using summary statistics (mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum), and categorically.

The number of investigational product applications by each subject based on diary data will be summarized using descriptive statistics.

The amount of investigational product used by each subject based on tube weight will be summarized by treatment using descriptive statistics, and categorically.

Investigational product application compliance will be calculated based on number of applications divided by the expected number (amount) of investigational product applications for each subject.

6.6. Safety Analysis

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. The safety population will be used for these analyses.

6.7. Adverse Events

All TEAEs occurring during the study will be recorded and classified on the basis of MedDRA terminology for the safety population. TEAEs are defined as those AEs with an onset on or after the time of first study drug application of the ARQ-151-313 study.

6.8. Local Tolerance Assessment

For Investigator's assessment, the numeric application site reaction scores will be summarized individually by using number and percentage of subjects by visit, as well as mean/median scores.

6.9. Clinical Laboratory Results and Vital Signs

All clinical laboratory results (subjects ≥12 years old) and vital signs measurements will be summarized descriptively by parameter, visit, and treatment group along with time point of collection.

A shift from baseline table describing out-of-normal range shifts will be provided for clinical laboratory results.

A shift from baseline table will identify subjects who gain or lose >5% body weight over the course of the study.

6.10. Prior and Concomitant Medications

Prior and concomitant medication information for all enrolled subjects will be presented in a by-subject listing. Summary tables will be presented by World Health Organization-Anatomical Therapeutic Chemical Classification System (WHO-ATC) therapeutic category and product.

6.11. vIGA-AD

The proportion of subjects who attain IGA scores of 0 or 1 and IGA success at each assessment time will be summarized. IGA scores will be summarized descriptively by visits over time.

6.12. EASI

EASI will be summarized descriptively by visits over time.

6.13. WI-NRS

WI-NRS will be summarized descriptively by visits over time.

6.14. Body Surface Area

Body surface area (BSA) affected by AD will be summarized descriptively by visits over time.

6.15. Subject Reported Outcomes Analyses

6.15.1. Dermatology Life Quality Index, Children's Dermatology Life Quality Index, IDQOL, SCORAD and POEM

Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), Infants' Dermatitis Quality of Life (IDQOL), the Dermatitis Family Impact (DFI), the Scoring Atopic Dermatitis (SCORAD), and the Patient-oriented Eczema Measure (POEM) will be analyzed by evaluation of the reduction in total score (change from baseline and percent change from baseline) by visits over time. These efficacy endpoints will be analyzed descriptively.

7. STUDY ADMINISTRATION

7.1. Ethics

7.1.1. Ethics Review Board

Before screening of subjects into the study, the current protocol, ICF/assent, and any accompanying material to be provided to the subjects will be reviewed and approved by an appropriate IRB or EC, as required by FDA (21 CFR § 56), Health Canada, and ICH GCP regulations. A letter documenting the IRB or EC approval must be received by the Sponsor (or delegate) before the initiation of the study at a clinical study site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, Sponsor, or designee will submit a progress report at least once yearly to the IRB. However, the frequency of these reports will depend on IRB or EC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or EC per the IRB requirements, and in compliance with FDA and Health Canada regulations and ICH GCP guidelines.

The Investigator, the Sponsor, or designee shall promptly notify the IRB or EC of any SAEs, SUSARs, or any other information that may affect the safe use of the study drug(s) during the study, per the IRB local requirements, and in compliance with FDA regulations and ICH GCP guidelines.

7.1.2. Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, the principles of the Tri-Council Policy Statement (TCPS), the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

7.1.3. Subject Information and Consent/Assent

The investigator is responsible for obtaining written informed consent from each individual participating in this study and/or their parents/caregivers after adequate explanation (in non_technical terms) of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB- or EC-approved consent form for documenting written informed consent. Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Each informed consent (or assent as applicable) will be read, appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or EC or local requirements.

Subjects will be given a signed copy of their ICF/assent.

7.2. Study Monitoring

Prior to the initiation of the clinical investigation, Sponsor representatives or designees may visit the clinical study site where the investigation is to be conducted. Sponsor representatives or designees shall ensure that the Investigator understands the investigational status of the investigational product, all requirements of the investigation to be undertaken, and all of his/her responsibilities as an Investigator. Sponsor representatives or designees will also visit the clinical study site at appropriate intervals as required to ensure compliance with the protocol and to verify the accuracy and completeness of data reported on the CRFs. The Study Director or designees shall be available for consultation with the Investigator and serve as liaisons between the clinical study site and the Sponsor.

The Sponsor or authorized designees may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) and investigational product dispensation logs for the subjects in this clinical investigation. The Investigator must permit access to such records. The Investigator must obtain, as part of informed consent, permission for an authorized representative of the Sponsor, or regulatory authorities, to review, in confidence, any records identifying subjects.

7.3. Study Completion and Termination

7.3.1. Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

7.3.2. Study Termination

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. An study site is considered closed when all required documents and study supplies have been

collected and a study site closure visit has been performed. The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further drug development.

7.4. Data Quality Assurance

In order to ensure the collection of accurate, consistent, complete, and reliable data during this clinical investigation, Sponsor representatives or designees may conduct audits of participating study sites at appropriate intervals throughout the study. The results of these periodic study site audits may be subject to review by independent auditors at completion of the clinical investigation.

All clinical data will undergo a quality control check prior to clinical database lock. Edit checks are performed for appropriate databases as a validation routine using SAS version 9.4 to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

7.5. Data Handling and Record Keeping

During the clinical study, the Investigator will maintain adequate source records, including medical records, records detailing the progress of the study for each subject, laboratory reports, signed informed consent forms, IP disposition records, correspondence with the IRB and Study Monitor/Sponsor, AE reports, and information regarding subject discontinuation and completion of the clinical investigation.

All required study data will be recorded on eCRFs. Any change of data will be recorded on the audit trail and a reason for the change will be entered.

The principal investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

7.6. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the investigator or Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and Sponsor.

Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s)/EC(s) will be promptly notified.

No deviation from the protocol will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor, and the IRB, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Sponsor and to the IRB(s)/EC(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan and Protocol Deviation Management Plan (PDMP).

No waivers to inclusion/exclusion criteria will be granted; subjects need to meet all criteria, exactly as specified, to be enrolled. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a subject in an emergency. Deviations that occur unintentionally or are the result of action by the subject must be documented and reported to the IRB(s)/EC(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan and PDMP.

7.7. Confidentiality and Privacy

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as date of birth) will be recorded on any form or biological sample submitted to the Sponsor. IRB [or] EC. The investigator agrees that all information received from Arcutis Biotherapeutics Inc., including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IP, and any other study information, remain the sole and exclusive property of Arcutis Biotherapeutics Inc. during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Arcutis Biotherapeutics, Inc. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

7.8. Conflict of Interest

All study investigators will provide documentation of their financial interest or arrangements with Arcutis Biotherapeutics, Inc., or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's participation in the study. All investigators with reported conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study.

7.9. Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

7.10. Publication Policy

The Sponsor is supportive of publishing clinical trial findings. Any form of publication that is derived from this study must be submitted to Arcutis Biotherapeutics, Inc. for review and approval. The process of coordinating publication efforts is detailed in the Clinical Trial Agreement.

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9. APPENDICES

APPENDIX 1. PATIENT HEALTH QUESTIONAIRE-8 (PHQ-8)

SMRC
Self-Management
Resource Center

Personal Health Questionnaire Depression Scale (PHQ-8)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
*(circle **one** number on each line)*

How often during the past 2 weeks were you bothered by...	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Scoring

If two consecutive numbers are circled, score the higher (more distress) number. If the numbers are not consecutive, do not score the item. Score is the sum of the 8 items. If more than 1 item missing, set the value of the scale to missing. A score of 10 or greater is considered major depression, 20 or more is severe major depression.

APPENDIX 2. PATIENT HEALTH QUESTIONNAIRE DEPRESSION SCALE (MODIFIED PHQ-A)

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an **"X"** in the box beneath the answer that best describes how you have been feeling.

	(0) Not at all	(1) Several days	(2) More than half the days	(3) Nearly every day
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				

APPENDIX 3. CHILDREN'S DEPRESSION INVENTORY 2 (PARENT REPORT)

By Maria Kovacs, Ph.D.

CDI 2 PARENT

Child's Name/ID: _____ Child's Sex: Male Female (Circle One)

Parent's Name/ID: _____ Date of Birth: ____/____/____ (Year / Month / Day)

Relationship to Child: _____ Today's Date: ____/____/____ (Year / Month / Day)

Child's Age: _____ Child's Grade: _____

Instructions:

For each of the statements below, select one response that best describes your observations of your child in the **past two weeks**.

Indicate your response for each item by **circling** the number that best corresponds to your choice. You may change an item response by drawing an X through your original choice and selecting a new response.

Remember, for each statement, pick **one** answer that best describes your observations of your child in the PAST TWO WEEKS.

My child...	Not at all	Some of the time	Often	Much or most of the time
1. looks sad.	0	1	2	3
2. has fun.	0	1	2	3
3. does not like himself or herself.	0	1	2	3
4. blames himself or herself for things.	0	1	2	3
5. cries or looks tearful.	0	1	2	3
6. is cranky or irritable.	0	1	2	3
7. enjoys being with people.	0	1	2	3
8. thinks that he or she is ugly.	0	1	2	3
9. has to push himself or herself to do schoolwork.	0	1	2	3
10. has trouble sleeping at night.	0	1	2	3
11. looks tired or fatigued.	0	1	2	3
12. seems lonely.	0	1	2	3
13. enjoys school.	0	1	2	3
14. spends time with friends.	0	1	2	3
15. is showing worse school performance than before.	0	1	2	3
16. does what he or she is told.	0	1	2	3
17. has disagreements and conflicts with others.	0	1	2	3

APPENDIX 4. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) "SINCE LAST VISIT" VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 5. VALIDATED INVESTIGATOR GLOBAL ASSESSMENT SCALE FOR ATOPIC DERMATITIS

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

APPENDIX 6. DERMATOLOGY LIFE QUALITY INDEX

DLQI

Site No: Date: Score:
Name:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No Not relevant	❒ ❒ ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒ Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒ Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much ❒ A lot ❒ A little ❒ Not at all ❒ Not relevant ❒

Please check you have answered EVERY question. Thank you.

APPENDIX 7. CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Site No.:
Name: Diagnosis: CDLQI
Age: SCORE:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, **school time?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school Very much Quite a lot Only a little Not at all Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

APPENDIX 8. INFANTS' DERMATITIS QUALITY OF LIFE INDEX (IDQOL)

Draft 7 **INFANTS' DERMATITIS QUALITY OF LIFE INDEX (IDQOL)**

Name: **Date:** **IDQOL SCORE** ☐
Address:

The aim of this chart is to record how your child's dermatitis has been. Each question concerns THE LAST WEEK ONLY. Please could you answer every question.

Dermatitis Severity

Over the last week, **how severe** do you think your child's dermatitis has been?; i.e. how red, scaly, inflamed or widespread.	Extremely severe	☐
	Severe	☐
	Average	☐
	Fairly good	☐
	None	☐

Life Quality Index

1.	Over the last week, how much has your child been **itching and scratching**?	All the time	☐
		A lot	☐
		A little	☐
		None	☐
2.	Over the last week, what has your child's **mood** been?	Always crying, extremely difficult	☐
		Very fretful	☐
		Slightly fretful	☐
		Happy	☐
3.	Over the last week approximately how much **time** on average has it taken **to get your child off to sleep** each night?	More than 2 hrs	☐
		1 - 2 hrs	☐
		15mins - 1 hr	☐
		0-15mins	☐
4.	Over the last week, what was the **total time** that your child's **sleep was disturbed** on average each night?	5 hrs or more	☐
		3 - 4 hrs	☐
		1 - 2 hrs	☐
		Less than 1 hour	☐
5.	Over the last week, has your child's eczema interfered with **playing or swimming**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
6.	Over the last week, has your child's eczema interfered with your child **taking part in** or **enjoying other family activities**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
7.	Over the last week, have there been problems with your child at **mealtimes** because of the eczema?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
8.	Over the last week, have there been problems with your child caused by the **treatment**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
9.	Over the last week, has your child's eczema meant that **dressing and undressing** the child has been **uncomfortable**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
10.	Over the last week how much has your child having eczema been a problem at **bathtime**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐

Please can you check that you have answered every question.

APPENDIX 9. DERMATITIS FAMILY IMPACT QUESTIONNAIRE (DFI)

Child's Name: **Mother/Father/Carer** **Date:** **Score**

The aim of this questionnaire is to measure how much your child's skin problem has affected you and your family OVER THE LAST WEEK. Please tick ☑ one box for each question.

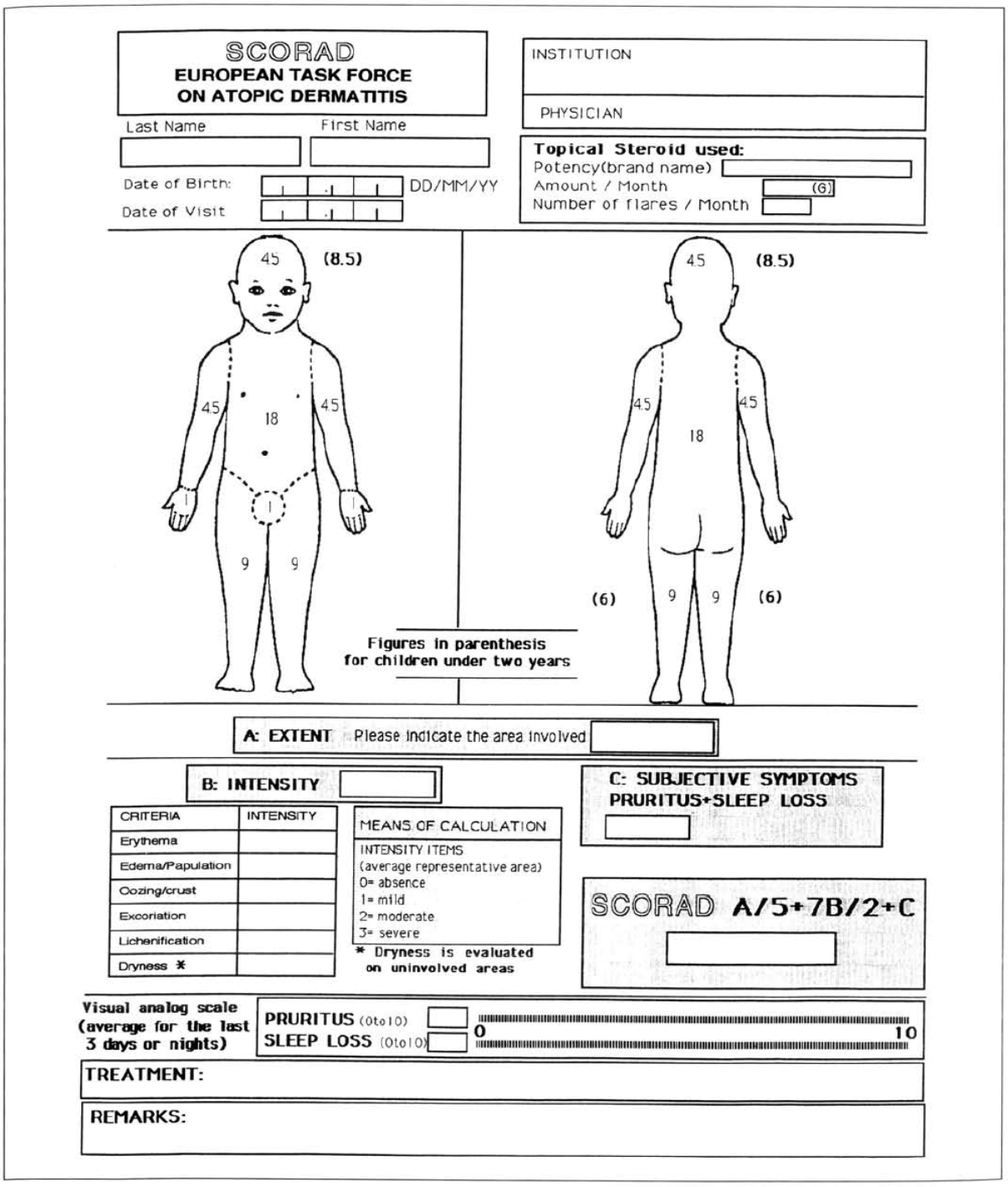
1.	Over the last week, how much effect has your child having eczema had on **housework**, e.g. washing, cleaning.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how much effect has your child having eczema had on **food preparation** and **feeding**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much effect has your child having eczema had on the **sleep of others in family**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
4.	Over the last week, how much effect has your child having eczema had on **family leisure activities**, eg swimming.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
5.	Over the last week, how much effect has your child having eczema had on **time spent on shopping for the family.**	Very much A lot A little Not at all	❒ ❒ ❒ ❒
6.	Over the last week, how much effect has your child having eczema had on your **expenditure**, eg costs related to treatment, clothes, etc.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
7.	Over the last week, how much effect has your child having eczema had on causing **tiredness** or **exhaustion** in your child's parents/carers.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
8.	Over the last week, how much effect has your child having eczema had on causing **emotional distress** such as depression, frustration or guilt in your child's parents/carers.	Very much A lot A little Not at all	❒ ❒ ❒ ❒

9.	Over the last week, how much effect has your child having eczema had on **relationships** between the **main carer and partner** or between the **main carer and other children** in the family.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
10.	Over the last week, how much effect has **helping with your child's treatment** had on the main carer's life.	Very much A lot A little Not at all	❒ ❒ ❒ ❒

Please check you have answered EVERY question. Thank you

APPENDIX 10. SCORAD

SCORAD https://www.ncbi.nlm.nih.gov/pubmed/8435513



APPENDIX 11. PATIENT-ORIENTED ECZEMA MEASURE (POEM)

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion and/or proxy completion

Patient Details: _____

_____

_____

_____ Date: _____

Please circle one response for each of the seven questions below about your/your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your/your child's skin been itchy because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

2. Over the last week, on how many nights has your/your child's sleep been disturbed because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

3. Over the last week, on how many days has your/your child's skin been bleeding because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

4. Over the last week, on how many days has your/your child's skin been weeping or oozing clear fluid because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

5. Over the last week, on how many days has your/your child's skin been cracked because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

6. Over the last week, on how many days has your/your child's skin been flaking off because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

7. Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

Total POEM Score (Maximum 28): .....

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion and/or proxy completion

How is the scoring done?

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

No days	= 0
1-2 days	= 1
3-4 days	= 2
5-6 days	= 3
Every day	= 4

Note:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored
- If two or more response options are selected, the response option with the highest score should be recorded

What does a poem score mean?

To help patients and clinicians to understand their POEM scores, the following bandings have been established (see references below):

• 0 to 2	= Clear or almost clear
• 3 to 7	= Mild eczema
• 8 to 16	= Moderate eczema
• 17 to 24	= Severe eczema
• 25 to 28	= Very severe eczema

Do I need permission to use the scale?

Whilst the POEM scale is protected by copyright, it is freely available for use and can be downloaded from: www.nottingham.ac.uk/dermatology
We do however ask that you register your use of the POEM by e-mailing cebd@nottingham.ac.uk with details of how you would like to use the scale, and which countries the scale will be used in.

References

Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective. Arch Dermatol. 2004;140:1513-1519

Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol. Dec 2013; 169(6): 1326–1332.

APPENDIX 12. NIAID DMID TOXICITY TABLE

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) Toxicity Table (2014) Modified

ABBREVIATIONS USED IN FOLLOWING TABLES:

Abbreviation/Term	Definition/Explanation
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AV block	atrioventricular block
bpm	beats per minute
BUN	blood urea nitrogen
CK	creatine kinase
CPK	creatine phosphokinase
FEV_1	forced expiratory volume in 1 second
g	Gram
HI	High
HPF	high power field
IU	international unit
IV	Intravenous
K/CUMM	$x10^3/mm^3$
LLN	lower limit of normal

Abbreviation/Term	Definition/Explanation
LO	Low
mEq	Milliequivalent
mmHg	millimeter of mercury
Ms	Millisecond
N	Normal
PT	prothrombin time
PTT	partial thromboplastin time
QTc	QT-interval corrected for heart rate
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
Rx	Therapy
S	Second
U	Unit
ULN	upper limit of normal

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**:	Transient or mild discomfort (<48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**:	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**:	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

CLINICAL ADVERSE EVENTS

Cardiovascular	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Arrhythmia		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required
Hemorrhage, blood loss	Estimated blood loss ≤100 mL	Estimated blood loss >100 mL, no transfusion required	Transfusion required
QTcF (Fridericia's correction)1 or QTcB (Bazett's correction)	Asymptomatic, QTc interval 450-479 ms, *OR* Increase in interval<30 ms above baseline	Asymptomatic, QTc interval 480-499 ms, *OR* Increase in interval 30-59 ms above baseline	Asymptomatic, QTc interval ≥500 ms, *OR* Increase in interval ≥60 ms above baseline
PR interval (prolonged)	PR interval 0.20-0.25 s	PR interval >0.25 s	Type II 2nd degree AV block *OR* Ventricular pause >3.0 s
Respiratory	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient-no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, acute	Transient wheeze; no treatment	Requires treatment; normalizes with bronchodilator and FEV_1 < 80% predicted before bronchodilator	Minimal normalization with bronchodilator andFEV_1 <80% predicted after bronchodilator
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment

[1] Inclusion dependent upon protocol requirements

Respiratory	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Nasal discharge (rhinitis infective per **CTCAE 4.0**)	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	-
Pharyngitis **(CTCAE 4.0)**	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Pneumonitis (rales or rhonchi) **(CTCAE 4.0)**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated
Lung infection (**CTCAE 4.0**)	-	Moderate symptoms; oral intervention indicated (e.g. antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated
Gastrointestinal	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours	6 or more loose or watery stools or >800 g/24 hours or requires IV hydration

Urinary Tract	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Urinary tract infection **(CTCAE 4.0)**	-	Localized; local intervention indicated (e.g. oral or topical antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Reactogenicity	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Local reactions			
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Erythema/redness [2]	2.5-5 cm	5.1-10 cm	>10 cm
Induration/swelling [3]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity
Systemic reactions			
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity

[2] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[3] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Reactogenicity	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All other conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

LABORATORY AND VITAL SIGNS TOXICITY GRADING (Some laboratory values have been modified to be consistent with the normal ranges of the ACM laboratory used in the present study)

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Sodium (mEq/L or mmol/L)	LO	131-<LLN	130	<130
	HI	>ULN-148	149-150	>150
Potassium (mEq/L or mmol/L)	LO	<LLN-3.2	<3.2-3.1	<3.1
	HI	>ULN-5.6	>5.6-5.7	>5.7
Glucose (mg/dL)	LO mmol/L	<LLN-3.0	<3.0-2.2	<2.2
	HI mmol/L	>ULN-8.9	>8.9-13.9	>13.9
Blood urea nitrogen	HI mmol/L	>8.9-17.8	>17.8-35.5	>35.5
Creatinine	N	115-151 (µmol/L)	152-177 (µmol/L)	> 177 (µmol/L)

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Calcium **(CTCAE 4.0)**	LO mmol/L	<LLN-2.0	<2.0-1.75	<1.75
	HI mmol/L	>ULN-2.9	>2.9-3.1	>3.1
Magnesium **(CTCAE 4.0)**	LO mmol/L	<LLN-0.5	<0.5-0.4	<0.4
Phosphorous **(CTCAE 4.0)**	LO mmol/L	<LLN-0.8	<0.8-0.6	<0.6
Creatine kinase (CPK or CK) **(CTCAE 4.0)**	HI	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN
Albumin	LO g/L	<30-28	<28-25	<25
Total protein	LO g/L	<LLN-52	<52-50	<50
Alkaline phosphatase (U/L) **(CTCAE 4.0)**	HI	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN
AST (U/L) **(CTCAE 4.0)**	HI	>ULN-3xULN	>3xULN-5xULN	>5xULN
ALT (U/L) **(CTCAE 4.0)**	HI	>ULN-3xULN	>3xULN-5xULN	>5xULN
Bilirubin, serum total (mmol/L) **(CTCAE 4.0)**	HI mmol/L	>ULN-1.5xULN	>1.5xULN-3xULN	>3xULN
Bilirubin, serum total (mg/dL) when ALT ≥105 (Hy's law)	HI	1.3-1.5	1.6-2.0	>2.0
Bilirubin, serum direct (mmol/L) (CTCAE 4.0)	HI mmol/L	>ULN-1.5xULN	>1.5xULN-3xULN	>3xULN
Amylase (U/L) **(CTCAE 4.0)**	HI	>ULN-1.5xULN	>1.5xULN-2xULN	>2xULN
Lipase (U/L) **(CTCAE 4.0)**	HI	>ULN-1.5xULN	>1.5xULN-2xULN	>2xULN

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Uric acid (mg/dL/mmol/L) **(CTCAE 4.0)**	HI	>ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences

[a] Depending upon the laboratory used, references ranges, eligibility ranges and grading may be split out by sex and/or age.

[b] Low, High, Not Graded (N).

[c] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.

Hematology	LO/HI/N [a]	Mild (Grade 1) [b]	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (women) (g/dL)	LO	10.8-11.3	9.2-10.7	<9.2
Hemoglobin (men) (g/dL)	LO	12.0-12.5	10.0-11.9	<10.0
White blood cell count (K/CUMM)	HI	11.00-15.00	15.00-20.00	>20.00
	LO	2.50-3.50	1.50-2.49	<1.50
Lymphocytes (K/CUMM)	LO	0.76-0.90	0.50-0.75	<0.5
Neutrophils (K/CUMM)	LO	1.50-1.95	1.00-1.49	<1.00
Eosinophils (K/CUMM)	HI	0.58-0.74	0.75-1.50	>1.50
Platelets (K/CUMM)	LO	120-130	100-120	<100
Coagulation				
Prothrombin time (PT, seconds)	HI	> ULN-14.4	14.5-15.7	>15.7
Partial thromboplastin time (PTT or aPTT, seconds)	HI	>ULN-42.1	42.2-50.0	>50.0
Fibrinogen (mg/dL) **(CTCAE 4.0)**	HI	>ULN-500	501-600	>600
	LO	<LLN-0.75xLLN	<0.75xLLN-0.5xLLN	<0.5xLLN
Urine				
Protein (dipstick)	HI	1+	2+	>2+
Glucose (dipstick)	HI	1+	2+	>2+
Blood (microscopic) - red blood cells per high power field (RBC/HPF)	HI	5-10 for males 9-10 for females	11-50	>50 and/or gross blood

[a] Low, High, Not Graded.

[b] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.

Vital Signs	LO/HI/N [a]	Mild (Grade 1) [b]	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C) [c]	HI	38.0-38.4	38.5-38.9	>38.9
Fever (°F)	HI	100.4-101.1	101.2-102.0	>102.1
Tachycardia - beats per minute	HI	101-115	116-130	>130 or ventricular dysrhythmias
Bradycardia - beats per minute	LO	40-45	35-40	<35
Hypertension (systolic) - mm Hg [d]	HI	141-150	151-160	>160
Hypertension (diastolic) - mm Hg	HI	91-95	96-100	>100
Hypotension (systolic) - mm Hg	LO	85-89	80-84	<80
Tachypnea - breaths per minute	HI	23-25	26-30	>30

[a] Low, High, Not Graded.
[b] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.
[c] Oral temperature; no recent hot or cold beverages or smoking. A protocol should select either °C or °F for inclusion.
[d] Assuming subject is awake, resting, and supine; for adverse events, 3 measurements on the same arm with concordant results.